ISSN: 2634 - 8861

Journal of Infectious Diseases & Case Reports

SCIENTIFIC Research and Community

Research Article

Open Access

Covid 19 Morbidity and Case Fatality Rate: An Analysis of Possible Confounding Factors

MARTINS Helder F B[1*], LOQUIHA Osvaldo[2], HANSINE Rogers[3], MACICAME Ivalda[4], MAURE Genito A[5], MARRUFO Tatiana J[6], SACARLAL Jahit[7], ABACASSAMO Fátima[8], MUCAVELE Helio[9] and SAÚTE Francisco C M[10]

[1]Medical Doctor, Specialist and Emeritus Professor of Public Health, PhD Honoris Causa in Health and Education Sciences, Former Minister of Health of the People's Republic of Mozambique (1975-80), Former Senior Official of WHO (1985-96), Former Member of several WHO expert committees.

[2]Biostatistics Specialist, Clinton Health Access Initiative. Assistant Professor of Statistics, Department of Mathematics and Informatics, Eduardo Mondlane University, Mozambique.

[3]MSc. in Development Studies, PhD in Human Geography, Lecturer and Assistant Researcher in the Department of Geography, Faculty of Arts and Social Sciences, Eduardo Mondlane University, Mozambique.

[4]MD, Researcher, Polana Caniço Health Research and Training Center (CISPOC) - National Institute of Health, Mozambique.

[5] Specialist in Climate Modeling, Assistant Professor, Faculty of Sciences, Eduardo Mondlane University, Mozambique.

[6]MD, Coordinator of the Health and Environment Program, including Occupational Health, National Institute of Health, Mozambique.

[7]MD, Epidemiologist, Associate Professor, Department of Microbiology, Director of the Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique.

[8]MD, Lecturer, Department of Community Health, Faculty of Medicine, Eduardo Mondlane University, Mozambique.

[9]Research Physician, Master in Epidemiology, Manhiça Health Research Center (CISM).

[10]MD, Epidemiologist, Scientific Director of the Manhiça Health Research Center (CISM).

ABSTRACT

Introduction: When the first report appeared of a protective effect of universal BCG vaccination on COVID- 19 morbidity and case fatality rates, as well as referring to previous papers on the nonspecific protective effects of BCG, our interest was raised, because Mozambique was in an unusual position in relation to BCG vaccination. Based on our knowledge of the history of global public health, we constructed a table with the number of cases of COVID-19 per 100,000 inhabitants and the case fatality rate of the countries that had carried out universal BCG vaccination for a long period (India, Japan and the ex-USSR countries), compared to countries without a universal BCG vaccination programme. We found that countries that had carried out universal BCG vaccination for a long period had much lower case/population ratios and case fatality rates than those without a universal BCG vaccination programme. This exercise was repeated three times, during the month of April, with consistent results. These results made us take the decision to undertake a study of possible confounding factors

Mozambique became independent in June 1975, and immediately after carried out a mass vaccination campaign with the six antigens of the recently created EPI. Smallpox vaccine was added, in order to consolidate smallpox eradication. WHO, at that time, was against vaccination campaigns, but an exceptional agreement was obtained. The campaign took place from the north to the south of the country, from February 1976 to January 1978. Every province started a routine EPI programme as soon as the campaign finished. In the campaign, all children 15 years old or younger received BCG vaccine. The coverage rate in the campaign was 97%, with 99% in the capital city of Maputo. Subsequently, the coverage rate of BCG vaccination at birth in the EPI has been always remarkably high in urban areas. In rural areas, coverage has been irregular, but has been at least 80% in the past 25 years. Therefore, most of the urban population aged 58 or less has received BCG, and so has an important part of the rural population. Such a high coverage of BCG is exceedingly rare in the world.

We have analysed the factors that may influence the development of COVID-19 epidemics and concluded that, apart from the virulence of the virus (that we do not have enough data to study), other factors are important, namely, the immune state of the population, the demographic profile and socioeconomic characteristics of the population, ecological and meteorological factors and, finally, the prevention measures taken and the degree of their implementation. Taking into consideration that most countries, with more or less firmness, have followed the WHO recommendations, on measures for prevention and control of COVID- 19, we decided not to analyse these measures. Our study therefore emphasised the other factors.

Methods: Our analysis focused on 82 countries, with more than 10 million inhabitants, which together correspond to 72.2% of the world population, distributed in three groups: northern hemisphere (above latitude 23º N), intertropical zone (between 23º latitude N and 23º latitude S) and southern hemisphere (below 23º latitude S). We have studied the relationship of BCG vaccination policies on the number of cases per 100.000 inhabitants and the case fatality rate, in the first 60 days and the first 90 days of the COVID-19 epidemics, in each country. We are performing bilateral and multilateral statistical analysis of variables related to climate (temperature, humidity and ultra-violet radiation), HIV prevalence and ART coverage, malaria (incidence and case fatality rate), tobacco and Vitamin D.

Results: The results are being analysed and will be published later.

Conclusions and Preliminary Recommendations: There is evidence of the non-specific protective effects of BCG, as well as negative statistical correlations on the malaria / COVID-19 ratio. However, there are still no conclusive proofs. There is scientific evidence on the beneficial effects of solar radiation (ultraviolet radiation) mediated by Vitamin D, which calms the cytokine storm caused by COVID-19.

The population is recommended to regularly expose themselves to the sun, using the slogan: "Take the sun staying at home". We also recommend the systematic administration of Vitamin D to all symptomatic cases of COVID-19 and that doctors be instructed on the appropriate doses of Vitamin D.

Declaration of No Conflict Of Interest: The authors have declared that they have not received any financing to perform this research and that they have no competing financial interests or personal relationships that could represent conflict of interest.

***Corresponding author**
Helder Fernando Brígido MARTINS, Medical Doctor, Specialist and Emeritus Professor of Public Health, PhD Honoris Causa in Health and Education Sciences, Former Minister of Health of the People's Republic of Mozambique (1975-80), Former Senior Official of WHO (1985-96), Former Member of several WHO expert committees, Mozambique. E-mail: helderfbm921@gmail.com

Received: September 01 2020; **Accepted:** September 09, 2020; **Published:** September 16, 2020

Introduction

The coronavirus disease (COVID-19), first reported in December 2019, in Wuhan, China, quickly became a pandemic presenting a global public health threat. With an exponential increase in the number of cases and deaths each day, this disease has already generated social disturbances, institutional breakdowns and major scientific uncertainties in the world.

Awakening our Interest in this Theme

At the end of March 2020, the international scientific community was surprised by an article1 by six researchers from the "Department of Biomedical Sciences, NYIT College of Osteopathic Medicine, New York Institute of Technology, Old Westbury, New York, USA". Even before it was published, the article was disseminated and went around the world.

These authors concluded that: "Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population" [1]. They also found that: "BCG vaccination also reduced the number of reported COVID-19 cases in a country [1]". Their final conclusion was that: "The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19" [1].

This article had huge media repercussions [2-14], with both the world scientific community and the mainstream media totally surprised. How was it possible that a vaccine used in humans since 1921 (exactly 99 years ago) could provide a solution for a disease that appeared about 3 months ago and that concerned all humanity.

The skepticism of the world scientific community was summarized in a statement by the Treatment Action Group (TAG) [15]: "Widespread media reports that the BCG vaccine may be protective against COVID-19 need to be read with caution. Results from randomized, controlled clinical trials are necessary to understand the role of this potential intervention before using BCG widely in an effort to stop COVID-19" [15].

The researchers were motivated to carry out the study in order to see if intercountry differences in case / population ratios and fatality rates from COVID-19 were related to BCG vaccination policy [1]. They had noted that countries such as Italy, USA, Lebanon, the Netherlands and Belgium, which never had a universal BCG vaccination policy and Iran, which only introduced universal BCG vaccination in 1984 (therefore only people under the age of 36 were vaccinated), had, at the time they began the study, high case/population ratios and fatality rates from COVID-19. While Japan and BrazilK, which had carried out universal BCG vaccination since at least 1947 had a low case / population ratio. These authors also compared Spain, which had a universal BCG vaccination policy for 16 years (1965 to 1981) with Denmark, which vaccinated for 40 years (between 1946 and 1986) and found large differences in the case / population ratios and fatality rates from COVID-19 [1]. They reported that they had analysed many countries, but do not list them [1].

This article aroused our curiosity as Mozambican researchers, because Mozambique is the African country with the largest number of age groups vaccinated by BCG, for reasons that will be explained later.

Based on our long experience in public health globally, we knew that the countries of the former USSR, Japan and India had practised a universal BCG vaccination policy for a long time (the countries of the former USSR since the late 1930s or early 1940s and Japan and India since 1947/48) and that they had not discontinued the use of the vaccine [16]. Eastern European countries had also introduced universal BCG vaccination from the late 1940s and early 1950s [16]. Only the Czech Republic had discontinued universal BCG vaccine use (in 2010).

Thus, on April 5th, we constructed a preliminary comparative table of case / population ratios and case fatality rates, of the countries of the former USSR, of Eastern Europe and a selection of other countries (Annex). Some of the included countries had never had a policy of universal BCG vaccination and others had practised the policy for at least 40 years.

Even without conducting an in-depth statistical analysis, the observation of the table in Annex showed that countries with no universal BCG vaccination policy had a much higher number of cases per 100,000 inhabitants and much higher case fatality rates compared to countries with a universal and consistent BCG vaccination policy. This table also shows that the countries that started BCG vaccination late or discontinued that policy for longer were in an intermediate position. In this sense, the Czech Republic, which discontinued BCG vaccination in 2010, stands out in relation to other countries in Eastern Europe, who had continued to vaccinate.

This table was repeated on 9th and on 15th April and the trends remained consistent.
Our interest in studying this topic therefore increased, because we knew that Mozambique was a unique case, in Africa and in the world, in relation to BCG vaccination policy.

Unusual Situation of Mozambique [17]:
Mozambique gained independence on 25 June 1975, about a year after the World Health Assembly adopted the famous Resolution WHA.27.57, which created the Expanded Program on Immunization (EPI) and recommended that it should be implemented throughout the world [18].

In the months preceding independence, an agreement had been laboriously negotiated with UNICEF, WHO and UNDP to carry out a huge national vaccination campaign, aimed at covering the entire national territory and the entire population [17].

UNICEF and UNDP agreed to finance the campaign, as long as WHO also agreed. WHO had just launched the EPI and was heavily opposed to vaccination campaigns. Laborious negotiation was required between the then Minister of Health of Mozambique and the Director-General of WHO. Finally, WHO agreement was, exceptionally, obtained and the campaign was able to take place [17].

At that time, the country only had sufficient technical personnel, to permit vaccination of three provinces at a time. The campaign, therefore, lasted two years, starting on the 26th, 27th and 28th February 1976, in the three northern provinces and ending on 2nd February 1978, in the City of Maputo (capital of the country, situated in the extreme South) [17].

In each province, routine EPI started as soon as the campaign ended [17].

The campaign was preceded by six months of intensive preparatory work and popular mobilization. This resulted in a coverage rate, calculated by experts from WHO and UNICEF, to be 97% for the country as a whole and 99% for Maputo City. This coverage was praised by the then Director-General of WHO, the late Dr Halfdan Mahler, as a success that had never before been achieved [17].

The start of routine EPI had problems and, in the first 2 years, the coverage rates left much to be desired, but by 1979, EPI was already well implemented, with high coverage rates [17].

BCG coverage rates have always been much higher than those of other vaccines (as is the case throughout Africa), as BCG is given in a single dose and at birth. If missed at birth, it is administered at the first contact of the child with the NHS.

A particularity of the campaign was that **BCG was administered to all children, from 0 to 15 years old** [17].

Although the age limit for BCG vaccination was 15 years, many adolescents over 15 were vaccinated, because the strong mobilization campaign led to a popular understanding that vaccines were good for health. Parents with children of 16, 17 or 18 years of age felt that their children should not be left out, so they gave a lower age [16].

From 1979 to 1992, the country was a victim of a war of destabilization, driven first by the minority Southern Rhodesian[L] regime of Ian Smith, and continued by the South African apartheid regime. This war particularly affected rural areas, where vaccine coverage rates dropped considerably. In urban areas they remained extremely high, as vaccines were readily available and many health personnel had fled to cities from insecure rural areas [16]. In Maputo City, coverage rates of 99.5% were recorded for several consecutive years [16].

We can conclude that the overwhelming majority of the urban population of Mozambique (where the COVID pandemic poses the greatest challenge), of less than 57-59 years old (depending on the province), has received BCG vaccination. A lesser proportion of the rural population of this same age group has also been vaccinated with BCG.

Very few countries in the world have such a large proportion of the population aged between 57 and 59 years vaccinated with BCG [19].

We concluded, therefore, that there were sufficient and consistent findings to build a hypothesis for a serious investigation on the topic of BCG and COVID-19. **This was how we got the idea for our investigation**.

Latest State of Knowledge
Although the initial article that motivated our interest in this subject was met with astonishment and skepticism by the international scientific community our bibliographic research showed us that these reactions were not justified [1,15]. The initial article itself states that: "Several vaccines including the BCG vaccination have been shown to produce positive "heterologous" or non-specific immune effects leading to improved response against other nonmycobacterial pathogens"[1]. The authors state that: "This phenomenon was named 'trained immunity' and is proposed to be caused by metabolic and epigenetic changes leading to promotion of genetic regions encoding for pro-inflammatory cytokines. BCG vaccination significantly increases the secretion of pro-inflammatory cytokines, specifically IL-1B, which has been shown to play a vital role in antiviral immunity" [1]. These conclusions were based on work by other authors, published in 2014 and 2016 [20,21] .

Therefore not only statistical findings show that universal vaccination with BCG can be effective in the fight against COVID-19, preventing progression to severe disease and death, but there is also an immunological and biochemical explanation [22-25]. BCG may have a non-specific protective action mechanism. This immunological and biochemical explanation represents a new and higher level of knowledge. We postulate that the astonishment and skepticism was mostly because these and other works on non-specific protective effects of BCG and on the 'trained immunity' were little known.

The authors of an article, cited in the initial article emphasize that the persistent and immunostimulatory properties of BCG strains differ, and their potential to induce trained immunity in vaccinated individuals may also vary [1,22]. They also analysed available data on BCG vaccine strains used in different countries, with Iran and China using the most modified, highly attenuated strains, deficient in methoxymycolic acids and with short-lived trained immunity, when compared with strains from Japan and Russia (vaccine used in Mozambique) [22].

Analysis of Factors That May Influence the Epidemic

Most of the scenarios that have been developed for Africa, both by European and American, academic centres, and by African institutions have failed to materialize, because they considered the preventive measures taken and the degree of their compliance, as well as the age structure of the population as, practically, the only factors influencing the course of the epidemic [26-31].

In our view, other factors are more important and should be considered: the degree of virulence of the SARS-CoV-2 virus, immune status, the demographic profile and socioeconomic characteristics of the population, ecological and meteorological factors and, finally, the preventive measures taken and the degree of compliance.

Let us look at some of those factors:

➢ **Degree of Virulence of the SARS-CoV-2**

The virus has shown varying degrees of virulence in different countries and over time in the same country [32,33]. In Mozambique, we have had cases imported from varied origins, which could result in the circulation of virus of varied virulence. We decided not to analyse varying virulence not only because of these circumstances, but also because we no enough data to evaluate it.

➢ **Immune status of the population**

African populations, as well as those in some Asian countries, are subject from birth to multiple infectious assaults resulting from poor hygiene, often due to lack of water and poor sanitation. Infections by multiple agents (bacteria, parasites, rickettsiae and viruses, etc.), result in high mortality rates, especially of neonates, infants and children, but survivors develop immunity and even group immunity. This has been named by an Indian scientist as the "Dirtiness Exposure Dividend" (DED) [34].

Studies published before the COVID-19 era, showed that helminth infections can induce the immune system to modulate inflammatory processes and that this has the potential to improve the control of viral infections, by limiting excessive inflammatory reactions [35,36]. Other authors studied how this modulation of inflammatory processes by helminths could alleviate allergic and autoimmune diseases [37].

There is still no solid bibliographic evidence of how helminth infections could contribute to controlling excessive inflammatory reactions in the case of COVID-19. There is, however, already a study that points out that «a reduced capacity for the production of proinflammatory cytokines and increased numbers of regulatory immune cells due to the immunomodulatory effects of pre-existing helminth infection could result in a reduced risk of severe COVID-19». This topic requires further investigation [38].

In 2018 Mozambique had the 8th highest country incidence of malaria in the world and a high m alaria case fatality rate [39]. The extent to which malaria can reinforce the mechanisms of non-specific immunity will be discussed later in this publication.

As we have already seen, African and Asian populations have been enjoying the benefits of vaccination carried out by the EPI. Some of the EPI vaccines, such as BCG and polio are live attenuated vaccines, and therefore more prone to stimulate non- specific protective effects. The non-specific protective effect of BCG is certainly the most frequently studied, with more details reported in the scientific literature [1,20,21,40-53].

We Therefore Chose BCG as the Central Point of our Investigation.

The role of Vitamin D in enhancing antiviral immunity will also be discussed later, in this publication.

Demographic Profile and the Socioeconomic Characteristics of the Population:

The demographic profile and the socio-economic context are important factors that can allow inferences about the trends in the health status of the population [54].

Regarding the age structure of the population in Mozambique, population pyramids show that the population structure is young. The 2017 population census indicated that the median age was 16.6 years and 53% of the population was under 17 years of age. Only 3.3% of the population was 65 years of age and over [55]. The same census data showed that 33.4% were residents of urban areas and 66.6% of rural areas [55]. Bearing in mind that COVID-19 tends to spread more easily in urban, than rural areas, the spatial distribution of the Mozambican population suggests that, only 1/3 of the population may be subject to the greater risk of infection associated with living in an urban area [56-59].

Some models and analyses have suggested that the case fatality rate of COVID-19 tends to be higher among older people [56,60]. The low proportion of elderly people suggests that levels of case fatality rate may be relatively lower in Mozambique.

For some authors the differences in the number of cases and deaths that occur between, as well as within countries, seem to be related to the age of individuals and even to their socioeconomic status [56,60,61]. In this sense, it is plausible that the demographic profile and socioeconomic characteristics of the population significantly influence the levels and trends in the morbidity and case fatality rate of COVID-19.

Although the demographic profile does not seem to be an important factor in spread, there is evidence to suggest that the fatality rate tends to be higher among countries with a high proportion of elderly in the population [58]. For instance, on the European continent, especially in the most affected countries, deaths are concentrated in older age groups [60]. For this reason, among the younger population in all countries, and among countries with a younger age structure, COVID-19 is expected to have relatively lower levels of lethality.

With regard to socio-economic issues, there are indications that among the most disadvantaged populations, especially in the poorest countries, a high number of cases and deaths may be reported [56]. Socioeconomic fragility is seen as limiting efforts to curb the spread of the virus, as socioeconomically less favoured people and countries may have limited access to resources which enable adequate health care [62].

Some authors suggest that other individual factors such as obesity, chronic diseases, lack of physical exercise and deficient nutrition also compromise immune capacity against the new coronavirus [63]. The case fatality rate could be higher in poor contexts, where nutrition tends to be deficient, but this has not always been seen in Africa. The hypothesis regarding the negative influence of socioeconomic inequalities that may affect health status, and in particular immune capacity, is consistent with the dynamics of the pandemic in the United States [64,65]. In this country, regardless of the age group, economic inequalities have had a strong influence on the disproportionate concentration of morbidity and case fatality rate among the most economically disadvantaged groups, specifically among African Americans. There are, however, other explanations for the higher incidence and case fatality rate among African Americans, as we will see later, in this publication.

➢ **Ecological and Meteorological Factors**

Ecological and meteorological factors are important in several diseases, in particular, communicable diseases and especially in communicable respiratory diseases [66] **his alone is sufficient justification to include these factors in our study**.

We carried out a rapid observation of the data provided to us daily by the various sites that report COVID-19 cases and deaths. Even without a deep statistical analysis, we could see that the countries of the intertropical region and of the southern hemisphere (who were in the summer in the first months of the pandemic) had a lower rate of cases and deaths than those of the northern hemisphere.

In order to have adequate control of outbreaks of this nature, it is essential that integrated surveillance systems and effective monitoring and prediction programs exist, linked to environmental determinants [67,68]. Recent studies reveal a possible link between outbreaks of infectious diseases and patterns of climatic variables [69,70]. But a recent exhaustive survey with peer review of the literature linking SARS-CoV-2 incidence to climate showed that studies linking SARS-CoV-2 incidence to climate on a global scale are scarce, limited and relatively recent.

Several attempts have been made recently to link epidemics to climatic or environmental determinants. For example, in an attempt to develop an early warning system for future epidemics in the Indian subcontinent and in Sri Lanka, a group of authors found statistically significant relationships between the El Niño-Sul oscillation and the historic malaria epidemics in that region [71]. Other authors have noted that environmental changes cause changing patterns of emerging parasitic diseases [72]. In a study on dengue, an empirical model was proposed that links the potential impact of population and climate change on the global distribution of dengue [73]. A localized experiment using guinea pigs as model hosts showed that transmission of the influenza virus depends on the relative humidity and temperature, with cold and dry environments favouring the transmission of the virus [74]. Further studies followed, linking relative humidity and temperature to the influenza virus, suggesting that the increase in the number of cases in winter is linked to immunodepression during this season.

The first study covering all countries affected by COVID-19, which analysed an association of COVID-19 with climate variables is quite recent. The authors found that, in Brazil, for COVID-19 infection, there was a negative association with average temperature and a positive association with precipitation. There was no association between deaths and temperature or precipitation [75]. Other recent studies, localized or limited to certain variables, also showed similar results [76,78]. In another recent study on the impact of climate and public health interventions on the COVID-19 pandemic, the authors reported that there were weak negative associations with relative humidity and absolute humidity, but little or no association between the growth of the epidemic and latitude and temperature [79].

Due to the scarcity of historical series, the existing scientific evidence, so far, is still not sufficiently robust for definitive conclusions about the influence of climatic factors. The literature does, however, indicate a link between climate and morbidity and mortality from coronavirus SARS-CoV- 2. Thus, to the variables already studied by other authors, we need to add other meteorological variables that may have a potential effect on the incidence of this virus globally. Solar radiation is one such variable, given its role as the main germicide in the environment and its potential to destroy RNA [80,81].

This component of our study includes, **for the first time at a global level**, ultraviolet (UV) radiation, along with temperature and relative humidity, to assess the extent to which the current global distribution of the virus is linked to the climate, in order **to determine their true influence or whether they are simple confounding factors**.

➢ **Preventive Measures Taken**

Many of the international authors have dedicated a large part of their analysis to comparisons of the way that measures to prevent the epidemic have been applied in different countries and have sought to draw conclusions.

But, in general, all countries have taken similar measures, recommended by WHO and derived from the recommended logical epidemiological measures to fight a highly contagious viral disease transmitted through the respiratory route [82,83].

The differences in practice were of a much lesser extent than speculated, and were mainly in the degree of intensity, firmness and timing.

A quick analysis of the evolution of the pandemic in different countries does not allow us to identify major differences in the way it unfolded, related to the measures taken. In Europe, there has been much speculation about the differences between the evolution of the pandemic in Sweden, which did not take severe mandatory isolation measures, and other European countries which took them. But the statistical data on cases, critical cases and deaths, shows no significant differences between the evolution of the pandemic in Sweden and other European countries.

In Africa, there are also no significant differences between the few countries that have strictly implemented mandatory isolation and those that have taken milder measures of civic education, without coercion.

In our opinion, given the socio-economic conditions of many Asian and African countries, including Mozambique, the application of strict measures of mandatory isolation is not possible. It would have serious consequences for the socio-economic life of the population, who, for the most part, practise a subsistence economy, incompatible with mandatory isolation. Statistical data do not show that countries that did not take coercive measures are more affected by the pandemic than those taking more stringent measures. Rather, the contrary has been shown.

Given these circumstances, **our study does not examine the effectiveness of implementation of prevention measures**.

List of Potential Confounding Factors

Aware that the statistical findings of a protective action of universal BCG vaccination on the number of cases and critical cases per 100,000 inhabitants and on the case fatality rate of COVID-19, do not by themselves represent causal relationships and may be confounded by other factors, we decided to analyse potential confounding factors, to determine their real influence. Thus, our analysis, in addition to studying the relationship between universal BCG vaccination and data on morbidity and case fatality rates of COVID-19, will also include the following factors

- Demographic profile and socioeconomic characteristics of the population,
- Ecological and meteorological factors,
- HIV and ART,
- Malaria,
- Tobacco,
- Vitamin D.

HIV and ART

In some of the analyses done based on the possible, more or less catastrophic scenarios of the evolution of the COVID-19 pandemic in Africa, fears were raised for countries with high rates of HIV seropositivity. The authors postulated that, due to the resultant weakened immune response, the affected countries could become victims of high morbidity and case fatality rates from COVID-19 [84].

Concerns were also expressed that the concentration of resources to combat the COVID-19 pandemic and people's fear of attending health units would greatly disrupt HIV/AIDS as well as Tuberculosis and Malaria programmes [85,86].

On the other hand, there were voices who considered that the antiretroviral treatment that HIV/AIDS patients are taking could have a protective effect in relation to SARS- CoV-2 [87].

Very recently, a group of authors who studied the relationship between COVID-19 and HIV in Spain, concluded that: «people living with HIV are not inherently more at risk for coronavirus infection than the general population, nor are they inherently more at risk for death or for experiencing a more severe course of COVID-19 relative to HIV- negative individuals» and that «HIV-positive patients receiving ARVT (TDF/FTC) have a lower risk for COVID-19 and related hospitalization than those receiving other therapies» [88-91]. A similar opinion is shared by other authors who claim that: «People living with HIV with well-controlled disease are not at risk of poorer COVID-19 disease outcomes than the general population» [89,92-95].

On the contrary, authors in South Africa concluded that COVID-19 patients with HIV and tuberculosis had higher mortality rates than those who did not have HIV or tuberculosis [96-101]. Two recent studies in the United Kingdom also found that: «HIV infection may be a risk factor for dying from COVID-19 but people with HIV without co-morbidities were not at increased risk» [102].

In View of These Diverse Opinions, We Decided to Include These Factors in our Analysis.

Malaria

Several articles emerged expressing fears that the COVID-19 epidemic would be a setback for malaria control programs in countries where it is endemic [103-107]. In general, these are low-income countries with fragile health systems.

An opposite view came from a blogger, who had a great media impact when announcing that a comparative statistical analysis of the indicators of morbidity and case fatality rates from COVID-19 showed that the countries most affected by malaria were the least affected by COVID-19 and vice versa [108]. Several articles followed showing that, in fact, the countries most affected by malaria were the least affected by COVID-19 and vice versa [109-111].

As Mozambique is one of the countries most affected by malaria, we felt that **we should include the possible protective effect of malaria in relation to COVID-19 in our study**.

The aforementioned blogger attributed this possible "protective effect of malaria" to the use of chloroquine in the treatment of this disease. Such an explanation cannot be entertained since chloroquine has ceased to be used in the prevention and treatment of malaria for about 40 years and the maximum time for plasma chloroquine elimination is 120 hours [108]. It can persist in certain tissues, but only for a maximum of 60 days [112].

Infection with Plasmodium falciparum induces a robust innate immune memory whose response can manifest itself in the form of hyper-response (training) or hypo-response (tolerance) and these changes are associated with epigenetic changes in innate immune cells [113-114]. This trained immunity protects against subsequent infections (reinfections) and is associated with a reduced risk of symptomatic malaria. However, there is still limited evidence that this trained immunity against Plasmodium falciparum can induce an enhanced response against unrelated microbial agents, such as happens with the hepatitis B virus, BCG and other live attenuated vaccines [115].

On the other hand, some studies suggest that Plasmodium falciparum infection and other infections, such as HIV, impair the adaptive immune response, causing atypical B memory cells and T-cell exhaustion [116-119].

Tobacco

Smoking is a recognized risk factor for severity and death from respiratory diseases [120]. Studies that explore the association between smoking and COVID-19 focus on the risk of infection, hospitalization for COVID-19 and severity during hospitalization [121].

A meta-analysis, analysing 7 studies, found a statistically significant association between smoking and the severity of COVID-19 disease [122].

A hospital-based study of 226 patients in Canada also showed that smoking was associated with a greater likelihood of admission to intensive care and death [123].

Given these findings, we found it advisable to include the influence of smoking in our study.

Vitamin D

The relationship between vitamin D and COVID-19 is explained by: «first, vitamin D supports production of antimicrobial peptides in the respiratory epithelium, thus making infection with the virus and development of COVID-19 symptoms less likely. Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2.» [124]. «Vitamin D is known to interact with a protein in this pathway— angiotensin-converting enzyme 2 (ACE2)—which is also exploited by SARS-CoV-2 as an entry receptor. While SARS-CoV-2 downregulates expression of ACE2, vitamin D promotes expression of this gene» [124].

The mean levels of vitamin D for 20 European countries and morbidity and mortality caused by COVID-19 were studied: «Negative correlations between mean levels of vitamin D in each country and the number of COVID-19 cases and deaths per million inhabitants were observed. Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19» [125,126].

Other authors found that de Vitamin D insufficiency is highly prevalent in severe COVID-19 illness [127]. This is because «Vitamin D also reduces the production of proinflammatory cytokines and Covid-19 infection gives rise to a "cytokine storm"» [128,132]. «Vitamin D influences several immune pathways, with the net effect of boosting mucosal defenses while simultaneously dampening excessive inflammation» [131]. Other authors stated that: «Correction of vitamin D deficiency is thought to suppress CD26, a putative adhesion molecule for Covid-19 host cell invasion. Vitamin D may also attenuate interferon gamma (IFNγ) and interleukin-6 (IL-inflammatory responses, both potent predictors of poorer outcome in critically-ill ventilated patients including those with Covid-19» [133]. Vitamin D may thus reduce COVID-19 mortality [129,131].

Vitamin D deficiency has also been shown to correlate with hypertension, diabetes, obesity and ethnicity—all features associated with increased risk of severe COVID-19 [129,134]. Vitamin D deficiency is likely compounded by skin pigmentation and age because aging decreases the ability of the skin to produce vitamin D3 [131].

When mortality per million is plotted against latitude, it can be seen that all countries that lie below 35 degrees North have relatively low mortality by COVID-19 [129-e131]. Thirty-five degrees North also happens to be the latitude above which little or no UVB radiation reaches the surface of the earth and therefore people do not receive sufficient sunlight to retain adequate vitamin D levels, during winter this is why, a substantial proportion of the population in the northern hemisphere, in these high latitudes, are currently vitamin D deficient [129-131]. This suggests a possible role for vitamin D in determining outcomes from COVID-19 [129-e131].

Some authors have suggested that the latitude dependence of death rates in COVID- 19 has a possible relationship to vitamin D deficiency [135]. They consider that Vitamin D status may influence the severity of response to Covid-19, and that the prevalence of vitamin D deficiency in Europe will be closely aligned to Covid-19 mortality [136].

Increasing use of sunblock and prevention of melanoma have resulted in lower levels of vitamin D in the winter months, especially in countries of higher latitude [128].

One author conducted a retrospective multicentre study of 212 cases with laboratory- confirmed infection of SARS-CoV-2 [137]. «Data pertaining to clinical features and serum 25(OH)D levels were extracted from the medical records. Serum 25(OH)D level was lowest in critical cases, but highest in mild cases. Serum 25(OH)D levels were statistically significant among clinical outcomes. Vitamin D status was significantly associated with clinical outcomes. The results suggest that an increase in serum 25(OH)D level in the body could either improve clinical outcomes or mitigate worst (severe to critical) outcomes, while a decrease in serum 25(OH)D level in the body could worsen clinical outcomes of COVID-19 patients» [137].

Researchers at Tel Aviv University studied 782 Covid-19 and 7,025 non-Covid-19 cases. They found that «the mean vitamin D levels were significantly lower in Covid-19 than non-Covid-19 cases. More importantly, low vitamin D levels increased the odds of hospitalization due to Covid-19 by 95%, after adjusting for demographics and comorbidities confounders» [138,139]. «Low plasma 25(OH)D level appears to be an independent risk factor for COVID-19 infection and hospitalization» the study authors concluded [138,139].

A group of researchers in Indonesia studied 780 cases of COVID-19, of which 380 died and 400 survived. Tracing back their medical records — looking for blood levels of vitamin D, any disease comorbidity, etc. — they detailed that «in dead cases: 46.7% has vitamin D deficiency; 49.1% had vitamin D insufficiency; the remaining 4.2% had normal vitamin D levels; in survived cases: 0.5% has vitamin D deficiency; 6.5% had vitamin D insufficiency; the remaining 93% had normal vitamin D levels. When adjusted for confounds — i.e., age, sex, and comorbidity — those with vitamin D insufficiency and deficiency were still 7.63 and 10.12 times more likely to die, respectively» [139,140].

«Older and male cases with a pre-existing condition and below-normal vitamin D levels were associated with increased odds of death» the researchers concluded [139,140].

«When controlling for age, sex, and comorbidity, Vitamin D status is strongly associated with COVID-19 mortality outcome of cases» [139,140].

In a retrospective study, researchers measured serum vitamin D levels in 134 people tested positive for Covid-19 in the UK. They found that only 19% (8/42) of patients admitted to an ICU had normal vitamin D levels. 39.1% (36/92) in those with non-ICU level severity had normal levels [139,141].

A recent meta-analysis of eight studies comprising 1,368 Covid-19 patients found a significant association between vitamin D insufficiency and severe Covid-19. «Patients with poor prognosis (N=634) had significantly lower serum levels of vitamin D compared to those with good prognosis (N=669), representing an adjusted standardized mean difference of -5.12», the study authors at Tulane University, in New Orleans, USA conclude [139,142].

A recently published complete and exhaustive review , of the relationships between Vitamin D, COVID-19 and associated co-morbidities, demonstrated unequivocally, the protective role of Vitamin D in controlling the hyper inflammatory state caused by SARS-CoV-2 (cytokine storm), as the «Vitamin D inhibits the production of proinflammatory cytokines and increases the production of anti-inflammatory cytokines» [143]. «Vitamin D exerts opposite effects on the adaptive (inhibition) and innate (promotion) immune system. This correlates with an anti-inflammatory response and balances the immune response». «Vitamin D may suppress T-cell mediated inflammation and stimulate Treg cells proliferation, by increasing IL-10 formation in DC cells, and thus enhance their suppressive effect» [143].

This article explains in detail the biochemical and immunological dysregulation mechanisms by which SARS-CoV-2 acts and how it worsens other co-morbidities (hypertension, cardiovascular disease, diabetes, obesity and acute respiratory distress syndrome - ARDS) that condition the severity of disease, and how Vitamin D has an antagonistic effect on these mechanisms [143]. The author of this work states that
«Vitamin D plasma level is an independent predictor of mortality» [143].
This author concludes: «There is ample evidence that various non-communicable diseases (hypertension, diabetes, CVD, metabolic syndrome) are associated with low vitamin D plasma levels. These comorbidities, together with the often-concomitant vitamin D deficiency, increase the risk of severe COVID-19 events. Much more attention should be paid to the importance of vitamin D status for the development and course of the disease. Particularly in the methods used to control the pandemic (lockdown), the skin's natural vitamin D synthesis is reduced when people have few opportunities to be exposed to the sun. The short half-lives of the vitamin therefore make an increasing vitamin D deficiency more likely» [143].

One author, who carried out an extensive and comprehensive bibliographic review, having analysed 141 articles considered that they «present primarily biological plausibility evidence overwhelmingly support the assertions that vitamin D sufficiency increases resistance to viral infections and helps prevent every symptom of severe Covid-19 that results in fatalities. They show that vitamin D deficiency can also explain every major risk factor, including the mystery of why children seem relatively protected and why males, the elderly, and people with naturally melanin-rich skin are especially vulnerable» [144].

Forty e seven of the studies analysed «demonstrate that vitamin D deficiency explains the geographical differences in Covid-19 case and fatality rates. They provide overwhelming correlational evidence for the hypothesis, and causal evidence as well. Covid-19 mortality was predicted by vitamin D in sixteen studies and vitamin D levels or sunlight predicted contracting Covid-19 in seventeen. Both causal modelling studies and eight chart reviews demonstrated that lower 25(OH)D was linearly associated with more severe Covid-19 outcomes» [144].

The author having studied «two causal modelling studies and several analyses of variance», considered that these studies «strongly supported the hypothesis that vitamin D deficiency is a causal, rather than a bystander factor, in Covid-19 outcomes» [144].

She considered that «there is already so strong evidence to support action» and she concluded that: «The evidence strongly suggests that vitamin D deficiency is an easily modifiable risk factor and correcting it is potentially life-saving» [144].

Note: A curious reported fact is that «During the "Spanish flu" pandemic of 1918- 1919, deaths were substantially reduced when patients were treated in "open air" hospitals with access to sunlight, perhaps due to vitamin D's "cytokine storm" suppression. In the deep south (USA), dramatically increased incidence of pneumonia led to much higher Spanish flu case fatality rates for African Americans than for whites» [144].

Taking all these findings into consideration, one author recommends: «Owing to the lack of specific treatment and urgency to act, these findings could justify the use of vitamin D as a possible adjuvant therapy. From the public health aspect, the recommendation of intensive supplementation as possible prophylaxis also could be considered» [126]. Similar recommendations are made by other authors [124,129,130,136,137,139,142-157]. One author states: «Although Vitamin D overdoses are theoretically possible, they are highly improbable» [144]. There are also authors who recommend determining the plasma level of Vitamin D in COVID- 19 patients admitted to hospitals [156,158].

Objectives of the Study

Taking all the above findings into account, we aimed to study the relationship between data on universal BCG vaccination and COVID-19 morbidity and case fatality rates in the first 60 days and 90 days of the pandemic's evolution, in 82 countries, of 10 million inhabitants or more, which together represent 72.2% of the world population.

At the same time, we will analyse other factors to determine whether they also influence COVID-19 morbidity and case fatality rates or whether they are simply confounders.

Methodology:

➢ **Type of Study**

Observational, analytical study, with a strong bibliographic review component.

➢ **Bibliographic Research Strategy**

As of April 1, 2020, a systematic literature review was made using the keywords ''COVID-19" and "BCG '', through Google Scholar, where it was possible to make use of official pages of CDC, NEJM, JAMA, Lancet, Cell, BMJ, Nature, Science, Elsevier, Oxford, Wiley and MedRxiv to search for scientific articles. In addition to this method, the search was also performed using the same keywords directly in the PUBMED and WHO Global database [159,160]. Primary, secondary research and meta- analyses were identified and included. Despite the preliminary nature of many reports and non-peer-reviewed articles issued during the COVID-19 pandemic, prepress documents and those from grey literature were also included in this review so as not to lose the information available on the subject. All articles and reports were analysed by content.

For the decision-making process in the case of disagreements, firstly, the disagreements found were recorded in order to understand their root cause. Then, the multicriteria method was adopted considering the following criteria: newer versus older articles, journal impact factor, frequency of keywords and relevance of the journal.

➢ **Country Eligibility Criteria (Inclusion / Exclusion)**

To select the countries for analysis, the number of inhabitants was used as the main criterion. The designations of countries and territories are the same as those used by the United Nations. Such designations are used in population projections and, therefore, are the same as those used in this work, to identify countries and territories whose population is equal to or greater than 10 million inhabitants [162]. Based on this criterion, 89 countries were identified and selected, corresponding to approximately 90% of the world population. Seven countries were excluded, namely: China, Democratic People's Republic of Korea, Tanzania, Syria, Somalia, Yemen and Sudan, although they have a population of 10 million or more.

China was excluded in view of the radical approach taken by this Asian country to contain the spread of the new coronavirus. The imposition of an early, strict and total confinement to a province is a measure that is unlikely to have been replicated in other contexts. The resultant impact on containing the virus merits emphasis as an important distinguishing factor between China and the rest of the world. As a result of this drastic measure, the disease ended up, in practice, being almost confined to one province, which has less than 10% of the country's total population. The Democratic People's Republic of Korea has not provided data on COVID-19 and there is no information on its BCG vaccination policy. Tanzania, for political reasons, has not provided recent systematic information on the evolution of the pandemic. This politically motivated lack of information seriously compromises data quality. Syria, Somalia and Yemen are countries that are in a state of war and have notable inconsistencies in the reported data, which may reflect the political situation. Sudan, too, has notable inconsistency in the reported data, with fewer tests performed than reported cases.

With the exclusion of these countries, the population covered by this study is over 5.6 billion people, which corresponds to 72.2% of the world's population. Spatially, 74.4% of the 82 countries that are part of the analysis are located in the northern hemisphere.

➢ Definition of Dependent / Independent Variables

➢ In relation to BCG

From the group of 82 countries selected for analysis, five subgroups of countries were created, based on their BCG vaccination policy:

- G1A - countries with a universal BCG vaccination policy for 40 years or more (20 countries),
- G1B - countries with a universal BCG vaccination policy for less than 40 years (25 countries),
- G1C - countries with a universal BCG vaccination policy but without information on the year of implementation (23 countries),
- G2 - countries that have discontinued universal BCG vaccination (9 countries),
- G3 - countries that have never adhered to universal BCG vaccination (5 countries).

➢ In relation to COVID-19

Three (3) indicators were calculated for the first 60 days and for the first 90 days after the first reported case of COVID-19, by country:

1. Number of tests, per 100 thousand inhabitants,
2. COVID-19 cases, per 100 thousand inhabitants,
3. Case Fatality rate (%).

➢ In Relation to HIV and ART

For all countries that met the inclusion criteria for the study, to obtain the most complete information possible, we searched for the presence of HIV-related variables that could be confounding factors, namely HIV prevalence and the coverage rate of antiretroviral treatment. To ensure that no country would be removed from this analysis, it was necessary to search different sources of information [163-166].

For comparative analysis, the two variables selected for HIV were included in the regression model. Each variable was classified in one of four groups using the UNAIDS, criteria [167,168].

Classification: HIV prevalence	
Low	<0.2%
Moderate Low	0.2 - 0.4%
Moderate High	0.4 - 1.0%
High	>1.0%
Classification: ART coverage	
Low	<44%
Moderate Low	44 - 60%
Moderate High	60 - 70%
High	>70%

➢ Data Collection / Extraction

☛ BCG data collection

- BCG vaccination policy data was collected from «The BCG World Atlas» [169].
- Of the countries that have at some point adopted an universal BCG vaccination policy, «The BCG World Atlas»provided information on the year of onset and the year of discontinuity, where applicable.
- Information on BCG vaccination coverage was obtained from the World Health Organization (WHO) Regional Office for Africa to confirm the year that universal BCG vaccination began in the countries under analysis from this region.
- For cases of divergent information between «The BCG World Atltas» and WHO, WHO data were considered [169].
- For Mozambique and Portugal, data from local, unpublished sources were used.

☛ COVID-19 Data Collection

Data were collected on COVID-19 for the first 60 days and the first 90 days of the pandemic after the notification of the first case, in each of the 82 countries selected for the study. Of these countries, Japan was the first to report a case of COVID-19, on 14 January 2020 and Burundi was the last, on 31 March 2020.

These periods of 60 and 90 days allowed us to establish a comparable time horizon dynamic of the epidemic in each country, taking also into account the prevention and control measures imposed. The cumulative number of positive cases and deaths and the cumulative number of tests performed up to the 60th and the 90th day of the pandemic in each country were extracted from the GIT HUB database [170,171].

☛Climatological Data Collection

The climate data used in this assessment was obtained from the European Centre for Medium-Range Weather Forecasts (ECMWF) ERA-5 [172]. These data provide the latest generation of global climate descriptions, with a spatial resolution of about 0.25x0.25 degrees (approximately 31km x 31km) and temporal resolution of one hour. Because not all countries in the world have homogeneous meteorological observation networks in space nor continuity in their time series, the data comes from a combination of climate models with observations, where these exist, from the national hydrology and meteorology services and through interpolations based on physical laws that represent climate processes, where observations do not exist. This objective combination of models and observations is called reanalysis and allows a determination of the values of climate variables anywhere in the globe, at any time, since 1979.

For this component of the study, global daily data of relative humidity (RH), temperature (Temp) and ultraviolet radiation (UV) were used to represent the average climate of 41 years, from 1979 to 2020, for the months of February to July and anomalies of each variable in the same period, for 2020.

These months were chosen because they represent the period that contains the beginning of COVID-19 case reports in most countries in the world.

➢ Statistical Analysis of Data

For this observational study, two main indicators were considered: the number of COVID-19 cases, per 100 thousand inhabitants and the case fatality rate (%), in the first 60 and the first 90 days of the epidemic, in each country.

The evaluation of the relationship between BCG and the main indicators, as well as the evaluation of potential confounding factors was done through generalized linear models with negative binomial distribution, using the main indicators as dependent variables and the co-factors as independent variables. For inference, the pre- established significance level was 5%. The data are being analysed using the R (R Foundation for Statistical Computing) software.

Results

The results are being analysed and will be published later.

Preliminary Conclusions

From the bibliographic research, we can already draw some preliminary conclusions

1. There is a lot of bibliographic evidence of the non-specific protective effects of BCG. There is still no conclusive proof, although studies already exist explaining the biochemical and immunological mechanisms of these effects. Some of these studies predate the COVID-19 era.
2. There are impressive negative statistical correlations on the malaria / COVID-19 ratio. The countries most affected by malaria are the least affected by COVID-19 and the most affected by COVID-19 are the least affected by malaria. This is not enough to establish causal relationships.
3. The first publications are also beginning to appear on a possible malaria-trained immunity effect, that could justify non-specific protective effects, but the scientific evidence in this regard is still too thin and scarce to draw conclusions.
4. There is scientific evidence, well documented in recent scientific literature, on the beneficial effects of solar radiation (ultraviolet radiation) mediated by Vitamin D.
5. The anti-inflammatory effect of Vitamin D (which was already known) is sufficiently demonstrated to provide some protection against COVID-19, leading to a benign course of the disease, with a marked decrease in the case fatality rate. The biochemical and immunological mechanisms of this protective effect of Vitamin D are well described in recent scientific literature.
6. In summary: Vitamin D, calm the cytokine storm caused by COVID-19, reinforcing the action of anti-inflammatory cytokines and attenuating the action of pro- inflammatory cytokines.
7. It is important to note that the tolerance of the human organism to high doses of Vitamin D is very large with only benign side effects described, only after taking very high doses of Vitamin D for prolonged periods of time.

Recommendations

Given these findings and at the present stage of our investigation, we make the following recommendations

- That the Information and Communication programs should include a recommendation for exposure to the sun, of a significant part of the skin, whenever possible, for 2 periods, of one hour each, between 10:00AM and 3:00PM.

We made this recommendation for African countries in which majority of population have high levels of melanin in their skin.

This recommendation is nor contradictory with the current recommendation of «Stay at Home!». The exposure to the sun can be done in backyards, on balconies or even on the street, in front of each house.

- The new recommendation can be «***Take the Sun, staying at Home***».

- Plasma levels of Vitamin D should be determined for all COVID-19 patients with symptoms.
- Vitamin D should be administered, in appropriate doses, to correct any Vitamin D deficiency.
- When it is not possible to determine vitamin D plasma levels, vitamin D should be administered systematically to all symptomatic cases of COVID-19.

As it is not certain that the majority of doctors know what Vitamin D doses to prescribe, we also recommend that:

- Doctors should be instructed on the appropriate doses of Vitamin D to prescribe.

Acknowledgments

We thank Mr. Vasco Américo Sambo for the invaluable collaboration he has given us to provide us with meetings by Zoom.

Annex: Ratio Population – Number of COVID 19 cases and Case Fatality Rate

Country	Population	Year	Nº of cases	Relationship Cases/Population	Case fatality rate
USSR (average)	293,941,600	2019	12,815	4.36/100,000	
Russia	146,795,000	2019	5,389	3.67/100,000	0.84%
Ukraine	42,180,000	2018	1,251	2.97/100,000	2.56%
Uzbekistan	33,337,000	2019	298	0.89/100,000	0.67%
Kazakhstan	18,396,000	2019	569	3.09/100,000	1.05%
Azerbaijan	9,975,000	2018	584	5.85/100,000	0.86%
Belarus	9,477,100	2018	562	5.93/100,000	1.42%
Tajikistan	8,931,000	2018	0	0/100,000	0
Kyrgyzstan	6,350,500	2018	147	2.31/100,000	0.68%
Turkmenistan	5,943,000	2019	0	0/100,000	0
Moldova	3,548,000	2018	752	21.20/100.000	1.86%
Armenia	2,970,000	2018	822	27.68/100,000	0.85%
Lithuania	2,794,000	2019	811	29.03/100,000	1.36%
Latvia	1,921,000	2019	533	27.75/100,000	0.19%
Estonia	1,324,000	2019	1,097	82.85/100,000	1.37%
Eastern Europe (average)	90,868,000	2018	13,913	15.31/100,000	
Poland	38,435,000	2018	3,834	9.98/100,000	2.19%
Romania	19,525,000	2018	3,864	19.79/100,000	3.83%
Czechia	10,640,000	2018	4,475	42.06/100,000	1.39%
Hungary	9,771,000	2018	733	7.50/100,000	4.64%
Bulgaria	7,051,000	2017	522	7.40/100,000	3.45%
Slovakia	5,446,000	2018	485	8.91/100,000	0.21%
Other countries					
USA	328,700,000	2019	311,637	94.81/100,000	2.71%
Italy	60,400,000	2019	124,632	206.34/100,000	12.33%
Spain	46,735,000	2018	130,759	279.79/100,000	9.50%
Iran	82,207,000	2019	58,226	70.83/100,000	6.19%
Portugal	10,292,000	2019	10,524	102.25/100,000	2.53%
South Africa	57,725,600	2018	1,585	2.75/100,000	0.57%
Nigeria	206,600,000	2019	224	0.11/100,000	2.23%
Japan	126,320,000	2019	3,139	2.48/100,000	2.45%
India	1,343,500,000	2019	3,588	0.27/100,000	2.76%

Countries of ex-USSR, of Eastern Europe, India, Japan and Nigeria are countries with universal BCG vaccination policy.

For the Cases / Population Ratio: Green: below 3/100,000 inhabitants; Yellow: between 3 and 20/100,000 inhabitants, Orange: between 20 and 75/100,000 inhabitants and Red: above 75/100,000 inhabitants. For the Lethality Rate: Green: Below 2.5%; Yellow: between 2.5 and 4%; Orange: between 4 and 7% and Red: above 7%.

Data Sources

Population data (except Nigeria): Wikipedia: List of countries by population. In: https://pt.wikipedia.org/wiki/Lista_de_países_por_população. Accessed at 5-04-2020.

Nigeria population data: United Nations Department of Economic and Social Affairs. In: https://countrymeters.info/pt/Nigeria. Accessed at 5-04-2020.

Data on cases, deaths and case fatality rate: OUTBREAK.My, In: https://www.outbreak.my/world. Accessed a 5-04-2020, at 3:00PM

References

1. MILLER Aaron, REANDELAR Mac Josh, FASCIGLIONE Kimberly, ROUMENOVA Violeta, LI Yan, et al. (2020) Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. Yale, In:https://doi.org/10.1101/2020.03.24.20042937.
2. STOCK Adobe (2020) The BCG vaccine against COVID-19 – really? INSERM Press Office, Paris, In: https://presse.inserm.fr/en/the-bcg-vaccine-against-covid-19-really/38920/.
3. DH: Coronavirus: More study needed on link of COVID-19 pandemic with BCG vaccine. Deccan Herald & PTI, New Delhi, https://www.deccanherald.com/national/coronavirus-more-study-needed-on-link-of-covid-19-pandemic-with-bcg-vaccine-820455.html.

4. FRANCE 24: Could TB vaccine protect medics from COVID-19? FRANCE 24, Paris, https://www.france24.com/en/20200403-could-tb-vaccine-protect-medics-from-covid-19.
5. SRUTHIJITH K K (2020) BCG vaccination policies make a ten times difference in COVID-19 incidence, mortality: New study. The Economic Times, New Delhi, In: https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/nations-without-bcg-vaccination-saw-higher-cases/articleshow/74956201.cms?from=mdr.
6. HOGG Alec (2020) Full interview, transcript: Is BCG-jab Covid-19's silver bullet? – NYIT's Dr Gonzalo Otazu. BizNews, Bangkok, https://www.biznews.com/inside-covid-19/2020/04/06/gonzalo-otazu-bcg-jab-covid-19.
7. O'SULLIVAN Kevin (2020) (Environment & Science Editor): Coronavirus: More 'striking' evidence BCG vaccine might protect against Covid-19. Study shows countries with vaccination programmes have far fewer cases. The Irish Times, Dublin, In: https://www.irishtimes.com/news/health/coronavirus-more-striking-evidence-bcg-vaccine-might-protect-against-covid-19-1.4222110.
8. PINKSTONE Joe (2020) Coronavirus death rate is SIX TIMES lower in countries that use the century-old tuberculosis BCG vaccine. MAILONLINE, London, https://www.dailymail.co.uk/sciencetech/article-8197247/Coronavirus-death-rate-SIX-TIMES-lower-countries-use-BCG-vaccine.html.
9. THE JAPAN TIMES (2020) Fewer coronavirus deaths seen in countries that mandate tuberculosis vaccine The Japan Times & BLOOMBERG, London, In: https://www.japantimes.co.jp/news/2020/04/09/world/science-health-world/fewer-coronavirus-deaths-seen-countries-mandate-tuberculosis-vaccine/#.XpSJo8gzbIU.
10. YU Gina (2020) How a 100-year-old vaccine for tuberculosis could help fight the novel coronavirus. CNN Health, Atlanta, https://edition.cnn.com/2020/04/09/health/tuberculosis-bcg-vaccine-coronavirus/index.html.
11. CAMERON Jackie (2020) Study that suggests BCG vaccine may protect against Covid-19 is flawed – TB experts. BizNews, Bangkok https://www.biznews.com/inside-covid-19/2020/04/10/bcg-vaccine-protect-covid-19-flawed.
12. MARTINEZ (2020) Marta Rodriguez & EURONEWS with AFP: Has the key to a coronavirus vaccine been staring us in the face for a century? EURONEWS & AFP, Lyon. In: https://www.euronews.com/2020/04/06/has-the-key-to-a-coronoavirus-vaccine-been-staring-us-in-the-face-for-a-century.
13. ADELSTEIN, Jake CHIAET Julianne (2020) TB vaccine offers hope in Covid-19 war. Asia Times, Tokyo https://asiatimes.com/2020/04/tb-vaccine-offers-hope-in-covid-19-war/.
14. MEDIAVILLA Daniel (2020) O mistério da velha vacina que parece prevenir a covid-19. El País, Madrid https://brasil.elpais.com/ciencia/2020-05-04/o-misterio-da-velha-vacina-que-parece-prevenir-a-covid-19.html.
15. TREATMENT ACTION GROUP (TAG) (2020) Statement on BCG Vaccine and COVID-19. TAG, New York, In: https://www.treatmentactiongroup.org/statement/treatment-action-group-statement-on-bcg-vaccine-and-covid-19/.
16. MARTINS Helder (2020) Personal Communication. Maputo.
17. MARTINS Helder (2020) "Descolonização das Vacinas". Presentation made on a cultural session of AMEAM (Associação dos Médicos Escritores e Artistas de Moçambique), in Maputo, on 18/12/2015.
18. OFFICIAL RECORDS OF THE WORLD HEALTH ORGANIZATION No. 217: TWENTY- SEVENTH WORLD HEALTH ASSEMBLY GENEVA, 7 -23 MAY 1974 PART I RESOLUTIONS AND DECISIONS. https://apps.who.int/iris/bitstream/handle/ 10665/85874/Official_record217_eng.pdf?sequence=1&isAllowed=y.
19. MARTINS Helder (2019) «Bringing to widespread Public Use latest Technologies and Innovations in Vaccines and Immunization: A Point of View from a Developing Country – Mozambique». Support Text for the presentation made on the: "32nd International Conference on Vaccines and Immunization". Roma (Italy).
20. KLEINNIJENHUIS J, Quintin J, Preijers F, Benn CS, Joosten LAB, et al. (2014) Long-lasting effects of bcg vaccination on both heterologous th1/th17 responses and innate trained immunity. J. Innate Immun. 6: 152-158.
21. NETEA M G, Joosten LAB, Latz E, Mills KHG, Natoli G, et al. (2016) Trained immunity: A program of innate immune memory in health and disease. Science 352: aaf1098–aaf1098.
22. GURSELA, Mayda, GURSEL Ihsan (2020) Is Global BCG Vaccination Coverage Relevant To The Progression Of SARS-CoV- 2 Pandemic? Med Hypotheses, In: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7136957/.
23. DAYAL, Devi and GUPTA, Saniya (2020) Connecting BCG Vaccination and COVID-19: Additional Data. Preprint MedRxiv, doi: https://doi.org/10.1101/2020.04.07.20053272.
24. OZDEMIR Cevdet, KUCUKSEZER Umut Can, TAMAY Zeynep Ulker (2020) Is BCG vaccination affecting the spread and severity of COVID-19? Allergy – European Journal of Allergy and Clinical Immunology (online), https://doi.org/10.1111/all.14344.
25. BERG Martha K, Qinggang Yu, Cristina E Salvador, Irene Melani, Shinobu Kitayama (2020) Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19. Preprint MedRxiv, doi: https://doi.org/10.1101/2020.04.05.20054163.
26. WALKER Patrick G T, WHITTAKER Charles, Oliver J Watson, Marc Baguelin, Peter Winskill, Et al. (2020) (Imperial College COVID-19 Response Team): The Global Impact of COVID-19 and Strategies for Mitigation and Suppression. Imperial College, London, Accessed on 5 Abril 2020. Later published in: Science 369: 413-422.
27. LSHTM CMMID COVID19 Working Group (2020) Modelling projections for COVID19 epidemic in Mozambique. LSHTM, London.
28. MOBS LABORATORY (2020) Northeastern University Boston, CIDID (Center for Inference and Dynamics of Infectious Diseases) & Fred Hutchinson Cancer Research Center, Seattle: Modeling local transmission and the burden of the COVID-19 epidemic in African countries. Boston e Seattle.
29. KISSLER S M, TEDIJANTO C, GOLDSTEIN E, Grad YH, Lipsitch M (2020) Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 368: 860-868.
30. FROST Isabel, Gilbert Osena, Jessica Craig, Stephanie Hauck, Erta Kalanxhi, et al (2020) COVID-19 in East Africa: National Projections of Total and Severe Infections Under Different Lockdown Scenarios. Washington, Center for Disease Dynamics, Economics & Policy, May 20, 2020. In: https://cddep.org/wp-content/uploads/2020/07/East-Africa-1.pdf.
31. CABORE Joseph Waogodo, Humphrey Cyprian Karamagi, Hillary Kipruto, James Avoka Asamani, Benson Droti, et al. (2020) The potential effects of widespread community transmission of SARS-CoV-2 infection in the WHO African Region: a predictive model. Brazzaville, World Health

Organization, Regional Office for Africa, May 2020. Later published in: BMJ Global Health 5: e002647.
32. BRUFSKY Adam (2020) Distinct Viral Clades of SARS-CoV-2: Implications for Modeling of Viral Spread. Journal of Medical Virology, In: https://doi.org/10.1002/jmv.25902.
33. HANG-PING Yao, Xiangyun Lu, Qiong Chen, Kaijin Xu, Yu Chen, et al. (2020) Patient-Derived Mutations Impact Pathogenicity of SARS-CoV-2. SSRN-Cell Press, Sneak Peak, 30 April 2020. In: https://doi.org/10.2139/ssrn.3578153.
34. KAMAT Nandkumar (2020) Hypothesis on COVID-19 Indian Subcontinental Dirtiness Exposure Dividend(DED). Taleigão, Goa University.
35. ROLOT Marion, Annette M Dougall, Alisha Chetty, Justine Javaux, Ting Chen, et al. (2018) Helminth-induced IL-4 expands bystander memory CD8+ T cells for early control of viral infection. Nature Communications 9: 4516.
36. HELMBY Helena (2009) Helminths and our immune system: Friend or foe? Parasitology International 58: 121-127.
37. MCKAY D M (2006) The beneficial helminth parasite? Parasitology 132: 1-12.
38. HAYS R, PIERCE D, GIACOMIN P, LOUKAS A, BOURKE P, et al. (2020) Helminth coinfection and COVID- 19: An alternate hypothesis. PLoS Negl Trop Dis 14: e0008628
39. WHO (World Health Organization) (2019) World Malaria Report Geneva: 2019. Licence: CC BY-NC-SA 3.0 IGO.
40. ROTH A, GUSTAFSON P, NHAGA A, DJANA Q, POULSEN A, et al. (2005) BCG vaccination scar associated with better childhood survival in Guinea-Bissau. Int J Epidemiol 34: 540-547
41. STENSBALLE L G, Ernesto Nante, Inge Panum Jensen, Poul-Erik Kofoed, Anja Poulsen, et al. (2005) Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea- Bissau: a beneficial effect of BCG vaccination for girls. Vaccine 23: 1251-1257.
42. NETEA M.G, QUINTIN J, VAN DER MEER JW (2011) Trained immunity: a memory for innate host defense. Cell Host & Microbe, 9(5):355-361.
43. WARDHANA, DATAU E A, SULTANA A, MANDANG VVV, JIM E (2011) The efficacy of Bacillus Calmette-Guerin vaccinations for the prevention of acute upper respiratory tract infection in the elderly. Acta Med Indones 43: 185-190
44. NETEA M G, VAN CREVEL R (2014) BCG-induced protection: Effects on innate immune memory. Seminars in Immunology 26: 512-517.
45. HOLLM-DELGADO M G, STUART E A, BLACK R E (2014) Acute lower respiratory infection among Bacille Calmette- Guérin (BCG)-vaccinated children. Pediatrics 133: e73-81
46. DE CASTRO M J, PARDO-SECO J, MARTINÓN-TORRES F (2015) Nonspecific (Heterologous) Protection of Neonatal BCG Vaccination Against Hospitalization Due to Respiratory Infection and Sepsis. Clin Infect Dis 60: 1611-1619.
47. JENSEN KJ, LARSEN N, BIERING-SORENSEN S, ANDERSEN A, ERIKSEN H B, et al. (2015) Heterologous immunological effects of early BCG vaccination in low-birth-weight infants in Guinea-Bissau: a randomized controlled trial. J. Infect. Dis 211: 956-967.
48. ARTS RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang SY, et al. (2018) BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe 23: 89-100.e5.
49. FREYNE B, Donath S, Germano S, Gardiner K, Casalaz D, et al. (2018) Neonatal BCG Vaccination Influences Cytokine Responses to Toll-like Receptor Ligands and Heterologous Antigens. J Infect Dis 217: 1798-1808.
50. MOORLAG SJCF, ARTS RJW, VAN CREVEL R, NETEA M G (2019) Non-specific effects of BCG vaccine on viral infections. Clin Microbiol Infec 1473-1478.
51. HEGARTY Paul, KAMAT Ashish M, ZAFIRAKIS Helen, DINARDO Andrew (2020) BCG vaccination may be protective against Covid-19. Preprint, In: https://www.researchgate.net/publication/340224580.
52. KURTHKOTI Krishna, NANDINI Dasgupta, GAUTAM Das (2020) Can BCG vaccination induced immune programming reduce the mortality in COVID-19 caused by SARS Cov2? Thiruvanathapuram e Mumbai. Pre-print, not yet published.
53. KLINGER Danielle, BLASS Ido, RAPPOPORT Nadav, LINIAL Michal (2020) Significantly Improved COVID-19 Outcomes in Countries with Higher BCG Vaccination Coverage: A Multivariable Analysis. Vaccines https://Doi:10.3390/vaccines8030378.
54. ARAÚJO Ana R L de (2001) Manual de Medicina para Estudantes de Medicina. (Centro de Estudos da População da Faculdade de Letras e Ciências Sociais (CEP-FLCS) UEM e Faculdade. de Medicina-Departamento de Saúde da Comunidade. Maputo, UEM – Imprensa Universitária, 2001.
55. INE (2019) IV Recenseamento Geral da População e Habitação de 2017: Resultados definitivos – Mozambique. Maputo, Instituto Nacional de Estatística.
56. AFRICA CENTER FOR STRATEGIC STUDIES (2020) Mapping Risk Factors for the Spread of COVID-19 in Africa. Washington, DC, AFRICA CENTER FOR STRATEGIC STUDIES, https://africacenter.org/spotlight/mapping-risk-factors-spread-covid-19-africa/.
57. CORBURN J, VLAHOV D, MBERU B, Riley L, Caiaffa WT, et al. (2020) Slum health: arresting COVID-19 and improving well-being in urban informal settlements. Journal of Urban Health 1-10.
58. BORJAS G J (2020) Demographic determinants of testing incidence and COVID-19 infections in New York City neighbourhoods. HKS Working Paper No. RWP20-008. Harvard Kennedy School. Cambridge, Massachusetts, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3572329.
59. SJÖDIN H, WILDER-SMITH A, OSMAN S, FAROOQ Z, ROCKLÖV J (2020) Only strict quarantine measures can curb the coronavirus disease (COVID-19) outbreak in Italy. Eurosurveillance https://doi.org/10.2807/1560-7917.ES.2020.25.13.2000280.
60. DOWD J B, ANDRIANO L, BRAZEL D M, ROTONDI V, BLOCK P, et al. (2020) Demographic science aids in understanding the spread and fatality rates of COVID-19. Washington, DC, Proceedings of the National Academy of Sciences 117: 9696-9698.
61. LIPP G, MATTIUZZI C, SANCHIS□GOMA RF, HENRY BM (2020) Clinical and demographic characteristics of patients dying from COVID□19 in Italy versus China. Journal of Medical Virology In: https://doi.org/10.1002/jmv.25860.
62. AHMED F, AHMED NE, PISSARIDE SC, STIGLITZ J (2020) Why inequality could spread COVID-19. The Lancet Public Health 5: e240
63. LIVINGSTON E, BUCHER K (2020) Coronavirus disease 2019 (COVID-19) in Italy. JAMA 323: 1335-1335
64. ALMAGRO M, ORANE-HUTCHINSON A (2020) The differential impact of COVID-19 across demographic groups: Evidence from NYC. https://ssrn.com/abstract=3573619 or http://dx.doi.org/10.2139/ssrn.3573619.
65. YANCY C W (2020) COVID-19 and African Americans.

JAMA 323: 1891-1892.

66. LIN K, YEE-TAK FONG D, ZHU B, KARLBERG J (2006) Environmental factors on the SARS epidemic: air temperature, passage of time and multiplicative effect of hospital infection. Epidemiol Infect 134: 223-230.
67. NAVA A, SHIMABUKURO JS, CHMURA AA, LUZ SLB (2017) The Impact of Global Environmental Changes on Infectious Disease Emergence with a Focus on Risks for Brazil. ILAR Journal 58: 393-400.
68. GESSNER BD, SHINDO N, BRIAND S (2011) Seasonal influenza epidemiology in sub-Saharan Africa: a systematic review. Lancet Infect Dis 11: 223-235.
69. ECCLES R (2002) An Explanation for the Seasonality of Acute Upper Respiratory Tract Viral Infections. Acta Oto-Laryngologica 122: 183-191.
70. SHAW Stewart PD (2016) Seasonality and selective trends in viral acute respiratory tract infections. Med Hypotheses 86: 104-119.
71. BOUMA MJ, VAN DER KAAY HJ (1996) The El Niño Southern Oscillation and the historic malaria epidemics on the Indian subcontinent and Sri Lanka: an early warning system for future epidemics? Trop Med Int Health 1: 86-96.
72. PATZ JA, GRACZYK TK, GELLER N, VITTOR AY (2000) Effects of environmental change on emerging parasitic diseases. International Journal for Parasitology 30: 1395-1405.
73. HALES S, DE WET N, MAINDONALD J, WOODWARD A (2002) Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. Lancet 360: 830-834.
74. LOWEN AC, MUBAREKA S, STEEL J, PALESE P (2007) Influenza virus transmission is dependent on relative humidity and temperature. PLoS Pathog 3: 1470-1476.
75. SOBRAL MFF, DUARTE GB, DA PENHA SOBRAL AIG, MARINHO MLM, DE SOUZA MELO A (2020) Association between climate variables and global transmission of SARS-CoV-2. Sci Total Environ.; 729:138997
76. PRATA DN, RODRIGUES W, BERMEJO PH (2020) Temperature significantly changes COVID-19 transmission in (sub)tropical cities of Brazil. Sci Total Environ 729: 138862.
77. SHI P, DONG Y, YAN H, Zhao C, Li X, et al. (2020) Impact of temperature on the dynamics of the COVID-19 outbreak in China. Sci Total Environ 728: 138890.
78. BASHIR M F, MA B, BILAL, Komal B, Bashir MA, et al. (2020) Correlation between climate indicators and COVID-19 pandemic in New York, USA. Sci Total Environ 728: 138835.
79. JÜNI P, ROTHENBÜHLER M, BOBOS P, Thorpe KE, Costa BRD, et al. (2020) Impact of climate and public health interventions on the COVID-19 pandemic: A prospective cohort study. CMAJ, https://doi:10.1503/cmaj.200920.
80. LYTLE CD, SAGRIPANTI JL (2005) Predicted inactivation of viruses of relevance to biodefense by solar radiation. J Virol 79: 14244-14252.
81. NORVAL M (2006) The Effect of Ultraviolet Radiation on Human Viral Infections. Photochemistry and Photobiology 82.
82. WORLD HEALTH ORGANIZATION (WHO) Coronavirus disease (COVID-19) advice to the public. In: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public.
83. WORLD HEALTH ORGANIZATION (WHO) Country & Technical Guidance - Coronavirus disease (COVID-19) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance.
84. CENTER OF DISEASE CONTROL AND PREVENTION (CDC:) (2020) What to Know About HIV and COVID-19. Atlanta https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/hiv.html.
85. VAUGHAN Adam (2020) How the covid-19 pandemic is making malaria and HIV more deadly. NewScientist HEALTH https://www.newscientist.com/article/2248423-how-the-covid-19-pandemic-is-making-malaria-and-hiv-more-deadly/.
86. JEWELL Britta L, MUDIMU Edinah, STOVER John, TEN BRINK Debra, PHILLIPS Andrew N, et al. (2020) SMITH, Jennifer A. et al.: Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. The Lancet HIV, published online http://dx.doi.org/10.1016/S2352-3018(20)30211-3.
87. FORD Nathan, VITORIA Marco, RANGARAJ Ajay, NORRIS Susan L, CALMY Alexandra, et al. (2020) Systematic Review of the Efficacy and Safety of Antiretroviral Drugs Against SARS, MERS or COVID-19: Initial Assessment. J Int AIDS Soc 23: e25489.
88. XU Zhe, ZHANG Chao, WANG Fu-Sheng (2020) COVID-19 in people with HIV. The Lancet HIV, Comment 7: E524-E526.
89. HELFAND Myles, SALZMAN Sony, MALEBRANCHE David (2020) HIV Care and Coronavirus (COVID-19): Info and HHS/CDC Recommendations for HIV/AIDS Clinicians. TheBodyPro, https://www.thebodypro.com/article/covid-19-cdc-recommendations-hiv-clinicians.
90. DREISBACH Eamon N, VOLBERDING Paul A (2020) People with HIV face similar risk for COVID-19 as general population. Haelio Infectious Disease, https://www.healio.com/news/infectious-disease/20200807/people-with-hiv-face-similar-risk-for-covid19-as-general-population.
91. DEL AMO J, POLO R, MORENO S, Díaz A, Martínez E, et al. (2020) Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy. Ann. Intern Med. Published online https://doi:10.7326/M20-3689.
92. COOPER, T. J.; WOODWARD, B. L.; ALOM, S. and HARKY, A.: Coronavirus disease 2019 (COVID-19) outcomes in HIV/AIDS patients: a systematic review. HIV Medicine, First published: 15 July 2020. In: https://doi.org/10.1111/hiv.12911.
93. BOERNER, Heather: HIV Does Not Appear to Worsen COVID-19 Outcomes. Medscape Medical News – Conference News – AIDS, July 02, 2020. In: https://www.medscape.com/viewarticle/933340.
94. MASOUD Zahra (2020) HIV Not Linked to Increased Risk for Severe COVID-19. InfectiousDiseaseAdvisor, https://www.infectiousdiseaseadvisor.com/home/topics/hiv-aids/hiv-not-linked-to-increased-risk-for-severe-sars-cov-2-infection/.
95. MASTROIANNI Brian (2020) COVID-19 Outcomes No Worse for Those Living with HIV. Healthline, Health News https://www.healthline.com/health-news/covid-19-outcomes-no-worse-for-those-living-with-hiv.
96. JERVING Sara (2020) South Africa data shows higher COVID-19 death rates for people with HIV, TB. Devex, Inside Development, COVID-19. https://www.devex.com/news/south-africa-data-shows-higher-covid-19-death-rates-for-people-with-hiv-tb-97447.
97. DAVIES Mary-Ann (2020) HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa. MedRxiv, preprint not been peer-reviewed. In: https://doi.org/10.1101/2020.07.02.20145185.
98. ABDOOL KARIM Aisha (2020) People living with HIV, TB at two to three-fold higher risk of COVID-19 death. Bhekisisa, https://bhekisisa.org/health-news-south-africa/2020-06-09-people-living-with-hiv-tb-at-two-to-three-fold-higher-risk-

of-covid-19-death/.
99. RYAN, Benjamin: HIV Emerges as Risk Factor for COVID-19 Death in South Africa. POZ, June 15, 2020. In: https://www.poz.com/article/hiv-emerges-risk-factor-covid19-death-south-africa. Accessed on 18/08/2020.
100. CLAYDEN Polly (2020) Update on Western Cape data: people with HIV have small increased risks from COVID-19. HIV i-Base https://i-base.info/htb/38266.
101. BERNARD, Rosie: Study finds increased risk of death from COVID-19 for people living with HIV and TB. AVERT, June 17, 2020. In: https://www.avert.org/news/study-finds-increased-risk-death-covid-19-people-living-hiv-and-tb.
102. ALCORN Keith, CAIRNS Gus (2020) Two UK studies find that HIV infection may be a risk factor for dying from COVID-19. NamAidsmap, https://www.aidsmap.com/news/aug-2020/two-uk-studies-find-hiv-infection-may-be-risk-factor-dying-covid-19.
103. DUNNING Hayley, VAN ELSLAND Sabine L (2020) COVID-19 pandemic could significantly increase HIV, TB and Malaria cases. Imperial College London Report. https://www.imperial.ac.uk/news/197257/covid-19-pandemic-could-significantly-increase-hiv/.
104. KRETCHMER Harry (2020) Malaria could make a comeback thanks to COVID-19. Davos-Klosters, Switzerland, World Economic Forum https://www.weforum.org/agenda/2020/04/malaria-treatment-rise-africa-coronavirus/.
105. KEYAMO-ONYIGE Ochuko (2020) COVID-19 and Malaria. New York, GBC Health – Corporate Alliance on Malaria in Africa (CAMA) http://www.gbchealth.org/category/news/.
106. FLETCHER Elaine Ruth (2020) Combined Impact of COVID-19 and Malaria Could Be 'Catastrophic', Warns Leading Research Group. In: https://healthpolicy-watch.org/combined-impact-of-covid-19-and-malaria-could-be-catastrophic-warns-leading-research-group/.
107. WHO – Global Malaria Programme (2020) The potential impact of health service disruptions on the burden of malaria: a modelling analysis for countries in sub-Saharan Africa. Genebra, WHO..
108. SPENCER Roy W (2020) Some COVID-19 vs. Malaria Numbers: Countries with Malaria have Virtually no Coronavirus Cases Reported. Roy Spencer's Home Blog. March 18th, 2020. In: http://www.drroyspencer.com/2020/03/some-covid-19-vs-malaria-numbers-countries-with-malaria-have-virtually-no-coronavirus-cases-reported/.
109. NAPOLI Pietro Emanuele, NIOI Matteo (2020) Global Spread of Coronavirus Disease 2019 and Malaria: An Epidemiological Paradox in the Early Stage of a Pandemic. Editorial – Journal of Clinical Medicine 9: 1138
110. MITCHELL Geoff, KHUDER Sadik (2020) Markedly Lower Rates of Coronavirus Infection and Fatality in Malaria-Endemic Regions – A Clue to Treatment? Elsevier – SSRN. https://ssrn.com/abstract=3586954.
111. MUNEER Azhar, KUMARI Kiran, TRIPATHI Manish, SRIVASTAVA Rupesh, MOHMMED Asif, et al. (2020 Sumit: Comparative analyses revealed reduced spread of COVID-19 in malaria endemic countries. MedRxiv preprint posted https://doi.org/10.1101/2020.05.11.20097923.
112. FUNDAÇÃO OSVALDO CRUZ (2020) Difosfato de cloroquina. Farmacocinética – DMG-FAR-PRO-CLO-000-2017. Farmanguinhos, Rio de Janeiro. https://www.far.fiocruz.br/wp-content/uploads/2017/02/Cloroquina-ProfSaude.pdf.
113. SCHRUM Jacob E, CRABTREE Juliet N, DOBBS Katherine R, KIRITSY Michael C, REED, George W, et al. (2018) Plasmodium falciparum induces trained innate immunity. J Immunol 200: 1243-1248.
114. RUSEK Paulina, WALA Mateusz, DRUSZCZYNSKA Magdalena, FOL Marek (2018) Infectious Agents as Stimuli of Trained Innate Immunity. Int. J. Mol. Sci https://doi:10.3390/ijms19020456.
115. BASSAT Q, MONCUNILL G, DOBAÑO C (2020) Making sense of emerging evidence on the non-specific effects of the BCG vaccine on malaria risk and neonatal mortality. BMJ Global Health 5: e002301.
116. PÉREZ-MAZLIAH D, NDUNGU FM, AYE R, LANGHORNE J (2020) B-cell memory in malaria: Myths and realities. Immunol Rev 293: 57-69.
117. MOIR S, FAUCI AS (2014) B-cell exhaustion in HIV infection: the role of immune activation. Curr Opin HIV AIDS9: 472-477.
118. WYKES MN, HORNE-DEBETS JM, LEOW CY, KARUNARATHNE DS (2014) Malaria drives T cells to exhaustion. Front. Microbiol 5: 249.
119. FENWICK C, JOO V, JACQUIER P, NOTO A, BANGA R, et al. (2019) T-cell exhaustion in HIV infection. Immunol Rev 292: 149-163.
120. PARK Ji-Eun, JUNG Soyoung, KIM Aeran (2018) MERS transmission and risk factors: a systematic review. BMC Public Health https://doi.org/10.1186/s12889-018-5484-8.
121. WORLD HEALTH ORGANIZATION (WHO:) (2020) Smoking and COVID-19. Scientific Brief. https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19.
122. ZHAO Qianwen, MENG Meng, KUMAR Rahul, Yinlian Wu, Jiaofeng Huang, et al. (2020) "The Impact of COPD and Smoking History on the Severity of Covid-19: A Systemic Review and Meta-Analysis," Journal of Medical Virology, In: https://doi.org/10.1002/jmv.25889.
123. KOZAK Robert, Karren Prost, Lily Yip, Victoria Williams, Jerome A. Leis, et al. (2020) Severity of Coronavirus Respiratory Tract Infections in Adults Admitted to Acute Care in Toronto, Ontario. Journal of Clinical Virology 126: 104338.
124. MITCHELL Fiona (2020) Vitamin-D and COVID-19: do deficient risk a poorer outcome? The Lancet Diabetes & Endocrinology, 8: 570.
125. ILIE PC, STEFANESCU S, SMITH L (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin. Exp. Res 32: 1195-1198.
126. JAKOVAC H (2020) COVID-19 and vitamin D-Is there a link and an opportunity for intervention? American Journal of Physiology - Endocrinology and Metabolism https://doi:10.1152/ajpendo.00138.2020.
127. LAU FH, Majumder R, Torabi R, Saeg F, Hoffman R, et al (2020) Vitamin D Insufficiency is Prevalent in Severe COVID-19. MedRxiv https://doi:10.1101/2020.04.24.20075838.
128. MOLLOY EJ, MURPHY N (2020) Vitamin D, COVID-19 and children. Ir Med J 113: P59.
129. RHODES JM, SUBRAMANIAN S, LAIRD E, KENNY RA (2020) Editorial: Low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. Alimentary Pharmacology and Therapeutics, 51: 1434-1437.
130. PANARESE Alba, SHAHINI Endrit (2020) Letter: Covid-19, and Vitamin D. Alimentary Pharmacology and Therapeutics 51: 993-995.
131. MARIK PE, KORY P,VARON J (2020) Does vitamin D status impact mortality from SARS-CoV-2 infection? Med.

Drug Discov 6: 100041.
132. DANESHKHAH Ali, AGRAWAL Vasundhara, ESHEIN Adam, SUBRAMANIAN Hariharan, KUMAR ROY, et al. (2020) The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID- 19 Patients. MedRxiv preprint paper. In: https://doi.org/10.1101/2020.04.08.20058578.
133. MCCARTNEY DM, BYRNE DG (2020) Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir. Med. J 113: P58.
134. CARTER Stephen J, BARANAUSKAS Marissa N, FLY Alyce D (2020) Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID‐19 Pandemic. Obesity 28: 1176-1177.
135. BRAIMAN Mark (2020) Latitude Dependence of the COVID-19 Mortality Rate—A Possible Relationship to Vitamin D Deficiency? SSRN Electron. J https://doi:10.2139/ssrn.3561958.
136. LAIRD E, RHODES J, KENNY RA (2020) Vitamin D and inflammation: Potential implications for severity of Covid-19. Ir Med J 113: P81
137. ALIPIO Mark M (2020) Vitamin D supplementation could possibly improve clinical outcomes of patients infected with Coronavirus-2019 (COVID-2019). Preprint of the author. Available at SSRN: https://ssrn.com/abstract=3571484 or http://dx.doi.org/10.2139/ssrn.3571484.
138. MERZON Eugene, Dmitry Tworowski, Alessandro Gorohovski, Shlomo Vinker, Avivit Golan Cohen, et al (2020) Low plasma 25(OH) vitamin D level is associated with increased risk of COVID‐19 infection: an Israeli population‐based study. The FEBS Journal https://doi.org/10.1111/febs.15495.
139. YONG Shin Jie (2020) Vitamin D as an Independent Risk Factor for COVID-19 Death. Microbial Instincts: preprint paper, https://medium.com/microbial-instincts/lack-of-vitamin-d-as-an-independent-risk-factor-for-covid-19-death-82365d0520fa.
140. RAHARUSUN Prabowo, PRIAMBADA Sadiah, BUDIARTI Cahni, AGUNG Erdie, BUD Cipta (2020) Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study. EMERGINNOVA, A preliminary study for early dissemination of results. In: https://emerginnova.com/patterns-of-covid19-mortality-and-vitamin-d-an-indonesian-study/.
141. PANAGIOTOU Grigorios, Su Ann Tee, Yasir Ihsan, Waseem Athar, Gabriella Marchitelli, et al. (2020) Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity. Clinical Endocrinology In: https://doi.org/10.1111/cen.14276.
142. MUNSHI Ruhul, Mohammad H Hussein, Eman A Toraih, Rami M Elshazli, Christina Jardak, et al. (2020) Vitamin D insufficiency as a potential culprit in critical COVID‐19 patients. J. Medical Virology https://doi.org/10.1002/jmv.26360.
143. BIESALSKI Hans K (2020) Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship? NFS Journal 20: 10-21.
144. BENSKIN Linda L (2020) Massive Review of papers on Vitamin D and COVID-19: A Basic Review of the Preliminary Evidence that Covid-19 Risk and Severity is Increased in Vitamin D Deficiency. ResearchGate preprint for publication in Frontiers in Public Health. https://vitamindwiki.com/Massive+Review+of+papers+on+Vitamin+D+and+COVID-19+-+July+3%2C+2020.
145. GRANT William B, LAHORE Henry, MCDONNELL Sharon L, BAGGERLY Carole A, FRENCH Christine B, et al. (2020) Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 12.
146. ISAIA Giancarlo, MEDICO Enzo (2020) Associations between hypovitaminosis D and COVID-19: a narrative review. Aging Clinical and Experimental Research https://doi.org/10.1007/s40520-020-01650-9.
147. LAIRD Eamon, KENNY Rose Anne (2020) Vitamin D deficiency in Ireland: Implications for COVID‐19. Results from the Irish longitudinal study on ageing. https://doi.org/10.38018/TildaRe.2020‐05.
148. HEDLUND Robert, DIAMOND Trude K, UVERSKY Vladimir N (2020) The latitude hypothesis, vitamin D, and SARS-Co- V2. Journal of Biomolecular Structure and Dynamics. Published online https://doi.org/10.1080/07391102.2020.1794973.
149. ALI Nurshad (2020) Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of Infection and Public Health, Available online In: https://doi.org/10.1016/j.jiph.2020.06.021.
150. ARBOLEDA John F, URCUQUI-INCHIMA Silvio (2020) Vitamin D Supplementation: A Potential Approach for Coronavirus/COVID-19 Therapeutics? Front. Immunol. 11:1523.
151. ANNWEILERA Cédric, CAOD Zhijian, SABATIERF Jean-Marc (2020) Point of view: Should COVID-19 patients be supplemented with vitamin D? Maturitas, Volume 140: P24-26.
152. RAZDAN Karan, SINGH Kuldeep, SINGH Dilpreet (2020) Vitamin D Levels and COVID-19 Susceptibility: Is there any Correlation? Med. Drug. Discov. Preprint paper, Jun 2, 2020. doi: 10.1016/j.medidd.2020.100051 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7266578/.
153. MAHDAVI Aida Malek (2020) A brief review of interplay between vitamin D and angiotensin‐converting enzyme 2: Implications for a potential treatment for COVID‐19. Medical Virology, Online Version, First published https://doi.org/10.1002/rmv.2119.
154. D'AVOLIO A, AVATANEO V, MANCA A, CUSATO J, DE NICOLO A, et al. (2020) 25- hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients 12: 1359.
155. DAVIES Gareth, GARAMI Attila R, BYERS Joanna (2020) Evidence Supports a Causal Role for Vitamin D Status in COVID- 19 Outcomes. MedRxiv preprint paper posted doi: https://doi.org/10.1101/2020.05.01.20087965.
156. EBADI Maryam, MONTANO-LOZA Aldo J (2020) Perspective: improving vitamin D status in the management of COVID- 19. Eur J Clin Nutr 74: 856-859.
157. MARTINEAU Adrian R, FOROUHI Nita G (2020) Vitamin D for COVID-19: a case to answer? The Lancet Diabetes-Endocrinology. Published online https://doi.org/10.1016/S2213-8587(20)30268-0.
158. IKEAGWULO RC, ETUKUDO HNS, OBETA Mark Uchejeso, MGBECHETA CU (2020) Does Vitamin D Serum Levels Affect the Risk of Covid 19 and its Clinical Outcomes? A Review of Literature. East African Scholars Journal of Medicine and Surgery https://doi: 10.36349/EASJMS.2020.v02i06.28.
159. GOOGLE SCHOLAR https://scholar.google.com/.
160. PUBMED https://pubmed.ncbi.nlm.nih.gov/.
161. WHO GLOBAL DATABASE https://www.who.int/gho/database/en/.
162. UNITED NATIONS (2019) Department of Economic

and Social Affairs (DESA), Population Division: World Population Prospects 2019, Online Edition. Rev. 1. https://population.un.org/wpp/Download/Standard/Population/.
163. WHO (2020) HIV Country Profiles 2019 https://cfs.hivci.org/country-factsheet.html.
164. UNAIDS-COUNTRIES (2020) https://www.unaids.org/en/regionscountries/countries .
165. TRADING ECONOMICS (2020) Venezuela - Incidence of HIV (% Of Uninfected Population Ages 15-49) https://tradingeconomics.com/venezuela/incidence-of-hiv-percent-of-uninfected-population-ages-15-49-wb-data.html.
166. PUBLIC HEALTH ENGLAND (2020) Prevalence of HIV infection in the UK in 2018. Health ProtectionReport, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843766/hpr3919_hiv18.pdf.
167. UNAIDS85 (2020) HIV Prevalence (Adults 15 – 49) http://aidsinfo.unaids.org/.
168. UNAIDS86 (2020) People living with HIV receiving ART (%) http://aidsinfo.unaids.org/.
169. MCGILL UNIVERSITY HEALTH CENTRE AND MCGILL UNIVERSITY TB CENTRE (2017) The BCG World Atlas, 2nd edition. Otava http://www.bcgatlas.org/.
170. BASE DE DADOS GIT HUB (2020) Cumulative number of positive cases and deaths recorded up to the 60th and 90th days of the pandemic, in each country. In: https://github.com/owid/covid-19-data/blob/master/public/data/owid-covid-data.xlsx.
171. BASE DE DADOS GIT HUB (2020) Cumulative number of tests performed up to the 60th and 90th days of the pandemic, in each country https://covid.ourworldindata.org/data/owid-covid-data.xlsx.
172. HERSBACH H, DEE D (2016) ERA5 reanalysis is in production, ECMWF Newsletter 147: 7.

Copyright: ©2020 Helder Fernando Brígido MARTINS. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.