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**ORIGINAL ARTICLE****Geographic Differences in the Spread, Morbidity and Mortality of COVID -19: Important Contributing Factors**

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**Abstract:**

The COVID-19 pandemic is creating a panic all over the world. By this time it has reached almost all countries causing variable morbidity and mortality in different countries. The mapping of COVID-19 pandemic shows a great difference in the spread of virus, morbidity and mortality. Several studies have shown that in middle high and high-income countries, its spread is very rapid and very high, and is associated with higher rates of morbidity and mortality. However, in developing countries and in most of the lower income countries, the spread of infection is comparatively very slow and is associated with comparatively lower morbidity and mortality. BCG vaccination policy, presence of more natural killer (NK) cells, killer immunoglobulin receptor (KIR) genes, repeated microbial infections, environmental factors, and malaria endemicity appear to be important contributing factors. Looking at these contributing factors, which are in favor of developing and lower income countries, the COVID-19 pandemic may not be very dreadful like affluent countries.

**Key Words:** COVID-19, Geographic differences, BCG vaccine, BCG vaccination policy, NK cells, KIR genes, Malaria endemicity

**Introduction:**

The COVID-19 pandemic is creating a panic all over the world. After its outbreak in China in December 2019, it is rapidly spreading and causing a large number of deaths. The disease has reached almost all countries in the world causing variable morbidity and mortality in different countries. When we look at the mapping of Corona virus infected cases in the different countries in the world, there are two different clear-cut zones showing difference in the spread of virus, morbidity and mortality caused by it. As per the current authentic figures available, the impact of spread of disease, its morbidity and mortality is different in different countries<sup>1,2</sup>. In some of the countries like Italy, Spain, France, United Kingdom (UK), United States of America (USA), China and other middle high and high income countries, its spread is very rapid and very high, and is associated with higher rates of morbidity and mortality. However, in countries like Japan, India, Russia, South Korea, Africa, Indonesia, and in most of the lower income countries, the spread of infection is comparatively very slow and is associated with comparatively lower morbidity and mortality, and almost negligible in most of the low income countries, of course with some exceptions to these observations<sup>1-3</sup>.

**Contributing factors:**

These geographic differences in the spread of infection, its morbidity and mortality are readily

appreciable when we look at the current figures of infected cases and number of deaths. The various scientific studies show that these differences may be attributed to various factors as below:

### 1. BCG Vaccination Policy

A recent study by Miller et al proposes that there is a definite correlation between universal Bacillus Calmette - Guerin (BCG) vaccination policy of the country with the slow spread of corona virus infection, reduced morbidity and mortality. The results of this study show that BCG vaccination policy of the country is an important contributing factor. This correlative study shows that those countries without universal BCG vaccination policy (USA, Italy, Netherland, etc.) have been found more severely affected with a large number of cases and higher mortality rates. However, countries with universal long-standing BCG Vaccination Policy (India, Japan, Brazil, etc.) have been found to have less number of COVID-19 cases and lower mortality rates. These results are in favor of proposal that BCG vaccination policy plays a significant role in reducing the morbidity and mortality associated with COVID-19<sup>3</sup>. Another study on evaluation of effect of BCG vaccination and COVID-19 information shows that BCG vaccine, in addition to inducing adaptive immunity against tuberculosis by activating T- cells also stimulates the components of innate immunity with the help of interleukin – 1 $\beta$  that helps to reduce viral infection significantly. It has been experimentally proved in both animal and human studies that the BCG vaccine produces non-specific effects on the immune system in addition to inducing immunity against tuberculosis. Although, the details of non-specific effects have not been characterized, it is known to boost the non-specific immune response against tumours by enhancing the cytotoxic activity of macrophages, T lymphocyte trapping, activating T lymphocyte and also by influencing B lymphocytes, and also known to induce immunity against, leprosy<sup>4-7</sup>.

### 2. The Natural Killer (NK) Cells

NK cells, a type of lymphocyte which can be differentiated as T or B lymphocytes, are the best known for killing of virally infected host cells. These are the components of innate immunity and are non-specifically directed against any virally infected host cell in our body. Their activity is stimulated by interferon and interleukin -2 produced by activated T-Cells. It has been reported that more number of NK cells are present in people from developing countries like India that makes their innate immunity comparatively stronger. NK cells are able to detect virally infected host cells and kill them, and thus, able to terminate the viral infection at an early stage of disease process<sup>8</sup>.

### 3. Killer Immunoglobulin Receptor (KIR) Genes

Killer cell Ig-like receptors (KIR) are responsible for controlling the immune response of NK cells and some T cells to infections and tumors. The NK cells use KIR in detecting infections and tumors. The KIR is involved in activating NK cells. These activating KIR genes have been shown to offer resistance to infections. The activities of these receptors are regulated by KIR genes, which are present in Indians as a result of natural selection to survive environmental challenges. Thus, activating KIR genes regulating activities of KIR and controlling the immunological response of NK cells may be another important contributing factor in controlling corona virus infection<sup>9</sup>.

### Repeated Microbial Infections

Repeated microbial infections, especially by commonly occurring viruses, parasites and bacterial pathogens in under developed and developing countries could be the reason for robust innate immunity that might be playing role in the fight against the corona virus infection, e.g. interferons - antiviral substances active against viruses, are nonspecifically produced by leucocytes, fibroblasts

and epithelial cells in response to repeated viral infections in under developed and developing countries and sometimes also formed in response to non-viral microorganisms might offer protection against corona virus infection<sup>6,7</sup>.

### 5. Environmental Conditions:

Environmental conditions have also been found to play role in spread of COVID-19. It is obvious from the present pandemic that spread of COVID-19 is rapid in cold countries where ambient temperature is less than 20°C or so; however, its spread in other countries where temperature is high appears to be comparatively less or very less.

### 6. Malaria Endemicity

Cases of COVID-19 have been reported from almost all malaria-endemic countries in all WHO regions. However, the spread of COVID-19 appears to be comparatively slower in these malaria endemic countries. Although, the exact casual relation between spread of COVID-19 in malaria endemic countries is not known<sup>2</sup>.

### Conclusion:

Looking at these contributing factors, which are in favor of developing, underdeveloped and lower income countries, the COVID-19 pandemic may not be very dreadful like as in developed/affluent countries.

It is obvious that almost all contributing factors, except BCG vaccination policy, have no scope to use them as a potential tool for fight against Corona Virus infection by changing or modifying them. In a current situation BCG vaccination policy is the only potential tool which can be easily implementable, safe and cost effective.

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