Review Article

# Exploring clues for wide variations in COVID-19 fatality rates among countries

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## Abstract

COVID-19 flu has been the worst pandemic on earth in more than a century and has thus far claimed more than six million lives worldwide. As of 19th March 2022, there were 57 major countries where one million or more COVID-19cases were registered, and the deaths reported therein constituted 92.3% of the total deaths worldwide. The high mortality rate is associated with comorbid conditions of the infected. Obesity, diabetes, cardiovascular diseases, high blood pressure, chronic obstructive pulmonary diseases, tuberculosis, and a higher percentage of the aged population (more than 65y) were identified as major morbidity conditions among others. Mycobacterium sensitized healthy people were found to resist the disease more efficiently. Prior vaccination with human influenza virus vaccines had considerable protective effects against catching or manifesting severity in COVID-19 flu. Timely vaccination with an approved vaccine against SARS-CoV-2 was considered immensely protective from the disease. All countries should therefore adopt policy measures that ensure adequate vaccination among their population.

**Keywords:** Comorbidities, coronavirus, COVID-19, innate immunity, macrophages, mycobacterium, obesity, SARS-CoV-2

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## INTRODUCTION

The pandemic created by COVID- flu the world over has brought unprecedented suffering to humankind. There were thirty-five countries as of October 22, 2021, that had one million people or more infected from the disease,[1] and the deaths per one million population in each country were different, varying from as high as over 5900 to as low as 3. This gap became wider with time. It was the endeavor to understand the probable causes for the wide variation. It was also explored if healthy individuals sensitized by infection and cured of certain bacterial and viral diseases widely prevalent in mankind the world over, such as tuberculosis and viral influenza could resist more efficiently the infection from SARS CoV-2 virus.

## STUDY METHODOLOGY

The study is based on a search of web pages of published literature on the internet of the Google Search Engine. The websites of the World Health Organization (WHO), major websites of governments of countries where high deaths from COVID-19 flu occurred, were consulted. Also, the websites of the Indian government departments involved in the administrative function, vaccination, R and D support,

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and funding of research on vaccines against the virus were consulted. The author has a background of hands-on experience in research and development, production and administration of drugs and pharmaceuticals, diagnostics, certain vaccines, and clinical chemistry reagents for several decades.

## Deaths analysis from COVID-19 flu (as of March 19, 2022)

To understand why there had been considerable variations in the number of deaths from COVID-19 flu, it is necessary to have first-hand information on the country wise disease load, the number of infected recovered, the number of deaths, the present number of active cases to understand if the disease is increasing or receding, and the number of deaths per one million population. Such information would be the starting point for probing into why the variations have been occurring. Such analysis may also provide clues on future courses of action to contain the disease more effectively. The following Table 1 provides the major country-wise information[2] on the above. The information collected was from all the countries where the total number of COVID-19 cases was one million or above. There were 57 such countries as of 19th March 2022. The information on China, being the largest populated country was also included. The total COVID-19 cases in these 58 countries were435.444 million and the total deaths from COVD-19 flu in these countries were 5630799, which was 92.4% (92.3% excluding China) of total deaths worldwide.

It can be seen from Table 1 that a maximum number of COVID-19 flu deaths had occurred in the USA, followed by another nine countries in decreasing order namely Brazil, India, Russia, Mexico, UK, Italy, Indonesia, France, and Iran. The total deaths in these ten countries up to March 19, 2022, from COVID-19, were reported at 3.611 million; this was about 59.2% of total reported global deaths from the disease. The disease which originated in the Wuhan city of China did not register high death rates in that country as the reported figures of deaths in China was only 4,638 numbers, and the death per one million population was only 3. The number of deaths per one million population in other nine countries, was 3053 in Brazil, followed by the USA (2983), Iran (2625), Italy(2613), Russia (2493), Mexico (2453), UK(2387), France(2150)Indonesia(551) and India(368).

Deaths can happen from all kinds of SARS-CoV-2 viruses causing COVID-19 flu. The disease, first reported on12 December 2019 from China, was later stated by the Chinese Authorities to cause 2,794 laboratory-confirmed cases of the disease by January 26, 2020, and had resulted in 80 deaths by then. The World Health Organization (WHO), China Country Office was informed of the cases of pneumonia (of then-unknown etiology) in China on December 31, 2019; later, on January 7, 2020, the virus was isolated and identified by the Chinese authorities, and on 12 January 2020they shared the genetic sequence of the novel coronavirus with the world.[3-5] By 20th January 2020, at least three countries (Thailand, Japan, and the Republic of Korea) reported the first cases in their territories! Thereafter, most parts of the whole world started getting the disease!.

In the meantime, based on previous other coronavirus infections, before 2019, it was determined that the RNA virus was prone to a comparatively fast mutation in its genomic sequence, and the mutation rate[6] was calculated to be $3.28 \times 10^{-4}$ per multiplication for Human coronavirus _229E. This implied that all the variants of this virus would have a mutation rate close to this rate. By September 2020, more than12000 mutants of the virus were reported.[7] The number of distinct mutants continued to rise over time. All the distinct mutants are classified based on the established, nomenclature by tracking SARS-CoV-2 genetic lineages and naming them by GISAID: (Global initiative on sharing all influenza data), Nextstrain, and Pango procedures. However, for simplicity, the World Health Organization (WHO), through its Technical Advisory Group on SARS-CoV-2 Virus Evolution, has come out with a simplified nomenclature using letters of the Greek Alphabet and has classified the mutants as (a)Variants of Concern (VOC), and (b) Variants of Interest (VOI), for identifying the main genomic traits of the variants among the common people. The mutants under VOC are named alpha, beta, gamma, delta, and omicron which were becoming more infectious in various regions of the world. This list continues to expand.

The information on the grouping of countries based on deaths per one million populations under different ranges, starting from 6000 and above per one million populations, gradually tapering down to one death per million populations, was compiled from the data in Table 1 and placed in Table 2. Also included in Table 2 is information about the country-wise population, 65yand above as % of their total population (2020).[8]

It is seen that a large number of countries had a very high incidence of the intensity of deaths over others.

***The apparent wide divergence in the above figures in Tables 1 and 2 drew the attention of the author to why such wide variations existed from country to country. It was the thought that if the factors responsible for such wide variations could be broadly identified and determined, then in the future years more effective intervention could be mounted to minimize such devastations.***

**Table 1: Countrywise total COVID-19 flu diseases up to March 19, 2022, in descending numbers for 58major countries**

| Sl. No | Country | Total Cases (million) | Total no. of Deaths | Total Recovered (millions) | ActiveCases (million) | Total Cases per one million population | Deaths per one million population | Ranking on number of deaths per one million |
|---|---|---|---|---|---|---|---|---|
| | World | 468.81 | 6,095,401 | 399.85 | 62.86 | 60,144 | 782.0 | |
| 1 | **USA** | 81.39 | 997,136 | 56.98 | 23.42 | 243,448 | 2,983 | 11 |
| 2 | **India** | 43.01 | 516,381 | 42.46 | 0.027 | 30,649 | 368 | 51 |
| 3 | **Brazil** | 29.58 | 656,867 | 28.16 | 7.56 | 137,476 | 3,053 | 9 |
| 4 | **France** | 23.96 | 140,841 | *22.51* | 1.31 | 365,655 | 2,150 | 24 |
| 5 | **UK** | 20.09 | 163,511 | 18.54 | 1.39 | 293,362 | 2,387 | 20 |
| 6 | **Germany** | 18.42 | 127,289 | 14.45 | 3.85 | 218,712 | 1,511 | 33 |
| 7 | **Russia** | 17.55 | 364,058 | 16.14 | 1.05 | 120,183 | 2,493 | 17 |
| 8 | **Turkey** | 14.66 | 97,077 | 14.29 | 0.27 | 170,728 | 1,130 | 37 |
| 9 | **Italy** | 13.72 | 157,607 | 12.45 | 1.12 | 227,564 | 2,613 | 15 |
| 10 | **Spain** | 11.32 | 101,703 | 10.57 | 0.65 | 242,053 | 2,174 | 23 |
| 11 | **S. Korea** | 9.04 | 12,101 | N/A | N/A | 176,045 | 236 | 53 |
| 12 | **Argentina** | 9.00 | 127,439 | 8.80 | 0.07 | 196,168 | 2,776 | 12 |
| 13 | **Netherlands** | 7.44 | 21,774 | *5.89* | 1.53 | 432,285 | 1,266 | 36 |
| 14 | **Vietnam** | 7.37 | 41,740 | 3.86 | 3.46 | 74,541 | 422 | 49 |
| 15 | **Iran** | 7.14 | 139,478 | 6.81 | 0.186 | 83,165 | 1,625 | 30 |
| 16 | **Colombia** | 6.08 | 139,415 | 5.91 | 0.0028 | 117,353 | 2,691 | 13 |
| 17 | **Japan** | 5.97 | 26,764 | 5.40 | 0.538 | 47,426 | 213 | 55 |
| 18 | **Indonesia** | 5.95 | 153,411 | 5.55 | 0.245 | 21,363 | 551 | 46 |
| 19 | **Poland** | 5.88 | 114,087 | 5.22 | 0.537, | 155,525 | 3,020 | 10 |
| 20 | **Mexico** | 5.63 | 321,931 | 4.92 | 0.385 | 42,896 | 2,453 | 19 |
| 21 | **Ukraine** | 4.93 | 107,477 | N/A | N/A | 113,850 | 2,483 | 18 |
| 22 | **Malaysia** | 3.95 | 34,244 | 3.62 | 0.294 | 119,481 | 1,035 | 39 |
| 23 | **Australia** | 3.86 | 5,722 | 3.47 | 0.385 | 148,555 | 220 | 54 |
| 24 | **Israel** | 3.75 | 10,417 | 3.70 | 0.041 | 402,214 | 1,117 | 38 |
| 25 | **Czechia** | 3.73 | 39,352 | 3.62 | 0.076 | 347,495 | 3,663 | 6 |
| 26 | **South Africa** | 3.70 | 99,868 | 3.59 | 0.015 | 61,105 | 1,648 | 29 |
| 27 | **Belgium** | 3.70 | 30,510 | *3.439* | 0.236 | 316,559 | 2,613 | 14 |
| 28 | **Philippines** | 3.67 | 58,023 | 3.57 | 0.045 | 32,781 | 518 | 47 |
| 29 | **Peru** | 3.54 | 211,751 | N/A | N/A | 104,874 | 6,273 | 1 |
| 30 | **Portugal** | 3.46 | 21,408 | N/A | N/A | 340,897 | 2,110 | 25 |
| 31 | **Austria** | 3.43 | 15,387 | 2.96 | 0.450 | 377,058 | 1,692 | 28 |
| 32 | **Canada** | 3.39 | 37,150 | 3.24 | 0.121 | 88,609 | 970 | 40 |
| 33 | **Chile** | 3.38 | 44,404 | *2.71* | 0.632 | 174,347 | 2,289 | 22 |
| 34 | **Thailand** | 3.33 | 24,165 | 3.07 | 0.238 | 47,490 | 345 | 52 |
| 35 | **Switzerland** | 3.25 | 13,467 | *2.61* | 0.630 | 371,323 | 1,537 | 31 |
| 36 | **Denmark** | 2.86 | 5,375 | *2.71* | 0.139 | 490,162 | 922 | 41 |
| 37 | **Romania** | 2.81 | 64,669 | 2.61 | 0.142 | 147,950 | 3,400 | 8 |
| 38 | **Greece** | 2.76 | 26,847 | 2.48 | 0.248 | 266,684 | 2,597 | 16 |
| 39 | **Sweden** | 2.48 | 18,020 | *2.40* | 0.057 | 242,554 | 1,765 | 27 |
| 40 | **Iraq** | 2.32 | 25,127 | 2.27 | 0.018 | 55,452 | 602 | 45 |
| 41 | **Serbia** | 1.95 | 15,662 | 1.90 | 0.041 | 224,958 | 1,805 | 26 |
| 42 | **Bangladesh** | 1.95 | 29,114 | 1.87 | 0.052 | 11,646 | 174 | 56 |
| 43 | **Hungary** | 1.82 | 44,961 | 1.67 | 0.106 | 189,644 | 4,674 | 3 |
| 44 | **Jordan** | 1.68 | 13,959 | 1.65 | 0.019 | 161,929 | 1,345 | 34 |
| 45 | **Georgia** | 1.64 | 16,643 | 1.60 | 0.028 | 412,817 | 4,186 | 4 |
| 46 | **Slovakia** | 1.63 | 19,093 | *1.48* | 0.125 | 297,912 | 3,494 | 7 |
| 47 | **Pakistan** | 1.52 | 30,328 | 1.48 | 0.016 | 6,667 | 133 | 57 |
| 48 | **Norway** | 1.38 | 2,169 | N/A | N/A | 250,517 | 395 | 50 |
| 49 | **Ireland** | 1.37 | 6,638 | *1.25* | 0.11 | 271,361 | 1,319 | 35 |
| 50 | **Kazakhstan** | 1.30 | 13,653 | 1.28 | 0.007 | 68,101 | 713 | 43 |
| 51 | **Morocco** | 1.16 | 16,050 | 1.146 | 0.0006 | 30,867 | 426 | 48 |
| 52 | **Bulgaria** | 1.12 | 36,266 | 0.894 | 0.193 | 163,693 | 5,287 | 2 |
| 53 | **Lebanon** | 1.09 | 10,237 | 1.02 | 0.057 | 160,541 | 1,511 | 32 |
| 54 | **Croatia** | 1.08 | 15,425 | 1.056 | 0.011 | 266,641 | 3,797 | 5 |
| 55 | **Cuba** | 1.08 | 8,504 | 1.069 | 0.0028 | 95,437 | 752 | 42 |
| 56 | **Tunisia** | 1.03 | 28,065 | 0.98 | 0.018 | 85,602 | 2,333 | 21 |
| 57 | **Hong Kong** | 1.016 | 5,401 | N/A | N/A | 133,794 | 711 | 44 |
| 58 | **China** | 0.128 | 4,638 | 0.105 | 0.019 | 89 | 3 | 58/125[a] |
| Total | | 435.444 | 5630799 | | | | | |

a=The rank of China based on this table is 58, but 125 based on all countries the world over

**Table 2: Deaths per one million population and 65y and above as percentage of total population (2020)**

| Death range per million population | No of countries | Name/s of country/ies(with numbers of people died per one million population)[% of the total population in 2020 that are 65y and above] |
|---|---|---|
| 6000 and above | 1 | Peru(6273) [8.73%] |
| 5000to 5999 | 1 | Bulgaria(5287) [21.47%] |
| 4000 to 4999 | 2 | Hungary(4674) [20.16%]; Georgia(4186) [15.25%] |
| 3000 to 3999 | 6 | Croatia(3797) [21.25%]; Czechea (3663) [20.14%]; Slovakia(3494) [16.70%]; Romania(3400) [19.23%];Brazil(3053) [9.59]; Poland(3020) [18.74%]. |
| 2000 to 2999 | 15 | USA(2983) [16.63%];Argentina(2776) [11.80%]; Columbia(2691) [9.06%]; Belgium(2613) [19.25%]; Italy(2613) [23.30%]; Greece (2597) [22.28%];Russia(2493) [15.51%]; Ukraine(2483) [16.95%]; Mexica(2453) [7.62%];UK(2387) [18.65]; Tunisia(233) [8.87%]; Chile(2289) [12.24%];Spain(2174) [19/98];France(2150) [20.75]; Portugal(2110) [22.77]. |
| 1000 to 1999 | 14 | Serbia(1805) [19.06%]; Sweden(1765) [20.33];Austria(1692) [19.20%];South Africa(1648) [5.51%]; Iran(1625) [6.56%]; Switzerland(1537) [19.10%]; Lebanon(1511) [7.55%];Germany(1511) [21.69%]; Jordan(1345) [3.95%]; Ireland(1319) [14.58%]; Netherland (1266) [20.03%]; Turkey(1130)[8.98%]; Israel (1117) [12.41%]; Malaysia (1035) [7.18%]. |
| 500to 999 | 8 | Canada (970) [18.10%]; Denmark (922) [20.16%]; Cuba (752) [15.89%]; Kazakhstan(713) [7.90%]; Hong Kong(711) [18.20%]; Iran (602) [6.56%]; Indonesia (551) [6.26%]; Philippines (518)[5.51%]. |
| 250 to499 | 5 | Morocco(426) [7.61%]; Vietnam (422) [7.87%]; Norway (395) [17.53%]; India (368) [6.57%]; Thailand (345) [12.96%]. |
| 100 to 249 | 5 | South Korea(236) [15.79%]; Australia (220) [16.21%]; Japan (213) [28.40%]; Bangladesh(174) [5.23%];Pakistan(133) [4.35%]. |
| 1 to 99 | 1 | China (3) [11.97%]. |
| Total | 58 | |

From the world figures of COVID-19 deaths in proportion to the number of cases reported worldwide [Table 1], it was found that only 1.3% of the infected had died. This figure can be used as the global case fatality rate (CFR) in March 2022. It was also revealed that globally, the death per one million population was782. Using these as the baseline figures, it was observed from the data in Table 2 that in very few countries (17 numbers only) death per one million was lower than the base figure; most countries registered death per one million populations between1000 and 3000(29 numbers); while a few (2 numbers) registered deaths of 5000 and above.

To ascertain what factors were responsible for such variations, initially, the various indices representing the status and standing of different countries were looked at to ascertain if any correlations existed between the indices and COVID-19 deaths. Other parameters such as pre-existing immunity against SARS-CoV-2 virus in blood; effect of vaccines and vaccination; and innate immunity status on exposure to certain microbial diseases like tuberculosis, viral influenza, etc were also looked into.

## Healthcare infrastructure index, pollution index, and cost of living index

In trying to understand if correlations existed between deaths per one million population and such factors as the ranks of countries in the Healthcare Infrastructure Index; Pollution Index; and Cost of Living Index, no trend[9,10] could be found. Countries with higher standards of Healthcare infrastructure index did not show lower deaths, nor death was lower for countries with low pollution index; nor was death lower in high Cost of Living Index countries.

## Whether pre-existing immunity against SARS-CoV-2 virus exists

On a question of whether pre-existing immunity against SARS-CoV-2 virus exists in B cells of individuals never previously exposed to the virus, humoral immunity in blood samples of adults collected during the pre-endemic period was analyzed. The binding and neutralization between the purified IgG generated from the samples did not show substantial activity against SARS-CoV-2. The results indicated that no pre-existing antibody and B cell immunity against SARS-CoV-2was in place[11] in SARS-CoV-2 virus unexposed adults. The virus-exposed population was, therefore, to acquire humoral immunity either through infection or through vaccination.

## Influenza virus vaccine and SARS-CoV-2 infection

It is known that the SARS-CoV-2 virus has a closer resemblance with multiple human influenza viruses in properties like methods and modes of transmission, related immune responses, certain clinical features, and even seasonal concomitancy and coincidence. The clinical syndromes in both the infection include symptoms like asymptomatic disease or mild influenza-like symptoms to severe pneumonia and acute respiratory distress conditions. The process of development of disease involving the immune response or components thereof as also the clinical features of both the virus types. have been compared on co-infected patients with COVID-19 and influenza. It was

concluded that co-infection can occur, and it was quite a challenge to diagnose the co-infected patients,[12] a situation where SARS-CoV-2 infection may be underdiagnosed. In another study, it was concluded that deployment of influenza vaccines may marginally protect[13] people from COVID-19 infection, which implies that perhaps exposure to multiple human influenza viruses through vaccination or infection and cure does not elicit significant activation of $CD4^+$ T cells and $CD8^+$ T cells in the Th-1 pathways against the COVID-19 flu viruses. Together, these studies indicate that human influenza viruses do not significantly contribute to protection from the SARS-CoV-2 virus.

However, since there is much resemblance between and among the multiple human influenza viruses and SARS-CoV-2 virus, [except that viral influenza is enveloped by negative-sense, single-stranded RNA viruses while SARS-CoV-2 viruses are enveloped by positive-sense RNA viruses], it was anticipated that human subjects resisting common human influenza viruses should have been tutored, and thereby acquired greater competence (earned by infection and cure, or by vaccination with multivalent inactivated or attenuated influenza viruses) to resist the SARS-CoV-2 viral infection. In one study in Brazil on 53752 clinically confirmed COVID-19 flu cases, it was statistically found that confirmed COVID-19 patients who received recent inactivated influenza vaccines experienced better health outcomes than patients who did not receive anti-influenza vaccines.[14]

The author thinks that innate immune cells tutored by influenza vaccination were the cause for getting better results in influenza vaccinated cohorts. The tutoring is thought to be linked to better recognition of the SARS-CoV-2 virus by the macrophages, activated through certain cytokines secreted by certain other innate immune cells while being sensitized by viral influenza vaccine antigens; more study is however required. In another study in Qatar, before the outbreak of COVID-19 in the country in an influenza vaccination campaign from September 15, 2020, to December 31, 2020, the 30774 health workers of the country were vaccinated with human influenza vaccines. This reduced COVID-19 infection among the influenza vaccine recipient health workers by 29.7%, while severe or critical, or fatal COVID-19 cases were reduced by 88.9%.[15]

In yet another study in a Dutch hospital, it was found that risk reduction in COVID-19 flu infection was substantial; the risk reduction was measured as 37% during the first wave and 49% during the second wave among the employees who were previously vaccinated with human influenza vaccines.[16]

From these studies, it is apparent that there is a substantial advantage in having prior vaccination of the deserving population with human influenza virus vaccines, both from increased protection from infection as well as from a reduction in severity in COVID-19 flu, if infected.

## Vaccines, vaccination, and immunity

Soon after the COVID-19 flu became established worldwide, scientists swung into action to come out with effective vaccines to protect the yet non-infected population. The issues were to develop, test, and obtain regulatory approvals for effective and safe vaccines. While the development of a new drug for treating an ailment takes a couple of years, the development of SARS-CoV-2 vaccines could not wait because of the deadly devastation the disease created, and on 11th December 2020, the United States Food and Drug Administration (USFDA) approved[17] the emergency use authorization of the mRNA vaccine of Pfizer-BioNTech against COVID-19 flu in the USA. Following this, several other countries came forward and accorded regulatory approval to various types of SARS-CoV-2 vaccines in their territories, based on safety and efficacy data generated by the vaccine developers. By the end of September 2021, worldwide there were 22 approved SARS-CoV-2 vaccines,[1] which rose[18] to 33 by the end of March 2022. These extraordinary developments contributed to the saving of millions of lives. One Report from the USA had concluded that all COVID-19 vaccines currently approved or authorized in the United States were effective against COVID-19 and had worked against the infection, manifesting benefits that included protection against COVID-19 flu, prevention from severe disease syndrome, hospitalization, and death.[19] Such benefits must have been accrued by all countries globally which had resorted to vaccinating their people with approved vaccines. Vaccines and vaccination had positively contributed to preventing deaths and preventing infection. However, as there is always a time lag between the development and deployment of vaccines on the population, and as vaccination has not yet reached every part of the deserving recipients for various reasons, the benefits of vaccination could not yet be rationally realized throughout the world.

From the chemical nature of the vaccinating antigens being researched, it is observed that the vaccines against the COVID-19 flu belong[1,20] to (a) the whole virus inactivated vaccines; (b) whole virus attenuated vaccines; (c) viral vector non-replicating vaccines;(d) viral vector replicating vaccines; (e) bacterial vector-based vaccines; (f) protein and peptide subunits- based vaccines; (g) virus-like particles-based vaccines; (h) DNA vaccines; (i) m RNA vaccines; and(j) vaccines based on monoclonal antibody fused to

SARS CoV-2 proteins. There are also a couple of host cells based vaccines. All these vaccines aim to strengthen and activate the three fundamental components of the adaptive immune system, namely the B cells (for producing neutralizing antibodies and to have memory B cells), the CD4+ T cells, and CD8+ T cells in both the Th-2 and Th-1 pathways.

## Innate immunity

Innate immunity in humans is the first system to defend the body from all kinds of damages that are likely to be encountered, which include detecting the invaders or damages in the body, rushing to the invaded/damaged sites, and getting engaged in activities to attack and destroy the invaders in cases of infection or initiate repairs in cases of damages identified as wounds/trauma. The innate immune system is enshrouded in certain white blood cells and includes dendritic cells, monocytes and macrophages, neutrophils, natural killer (NK) cells, basophils, eosinophils, Langerhans cells, and mast cells in the hematopoietic cells system. Non-hematopoietic cells include the epithelial cells residing on the skin, gastrointestinal tract, and airways, which also mount innate immune responses.

Innate immunity capacitates the infected individuals to mount resistance almost instantaneously, as the infecting agents like viruses get access to the cells by crossing the plasma membranes at the infecting sites. While the innate immune system works independently to attack the invaders, it also sends molecular messages to the adaptive immune system to get activated to defend against the invaders.

It is necessary to run through and reprise the thought processes, evidence, and scientific understanding of how innate immunity developed in eukaryotic life forms. It is worth recapitulating that on an estimated age of the earth of $4.54 \pm 0.05$ billion years, life may have appeared between 4.41 to 3.42 billion years ago, following the formation of oceans some 4.5 billion years ago and thereafter, about 2.7 billion years ago the eukaryotes may have evolved.[21-23] Initial simple life forms are thought to be the prokaryotes (tiny bacteria and archaea). Eukaryotes are thought to have arisen from prokaryotic ancestors through stages of multiple endosymbiosis. Eukaryotes evolved and differentiated into complex multicellular life forms, with multiple cellular tissue organization, where the tissues got interwoven, creating cellular connections through pores and complex protein structures interconnected with one another, and making the flow of cellular fluids like blood. Such fluids were created to feed each cell at their residence, carrying nutrients to the cellular doors, continuously clearing the debris, generated by the cellular activities, and sending such debris outside of the body through other mechanisms. Innate immune cells were evolved and posted at every vital corner of the stationary tissues to protect those from attack by the invading pathogens. In this long journey of evolution, spanning a few billion years when and how the innate immune system got developed in humans and evolved more towards perfection are issues enshrouded in conjectures and imaginations. The human species is thought to be evolved from Homo sapiens, and the latter may have evolved from their early hominid predecessors about 200,000 years ago.[24] Interestingly, from primitive vertebrates to humans, all use innate and adaptive systems to defend against pathogens; as more complex eukaryotes evolved in the evolution process, the innate immune system got more sharpened to recognize the pathogens and destroy those through complex biochemical and biological responses. In the evolutionary process, there seem to be several missing links from the formation of simple prokaryotes to complex multicellular eukaryotic life forms which are yet not resolved.

Every pathogen has certain portions of its genome, which are conserved and remains intact, bearing the firm identity of the pathogen in the species, which is characterized by genotypic, phenotypic, and phylogenetic criteria. Such firm genomic portions transcribe and translate into proteins which are the conserved determinants of the pathogens. Besides conserved nucleotide sequence portions, pathogenic microbes may also have distinct microbial cell walls, metabolic secretion products, and other such products that distinguish them from others. These substances can be identified by the receptors of the eukaryotes. Receptors for recognition reside in the innate immune cells of higher organisms, which get activated on encountering the pathogenic determinants, and a series of signaling events get triggered to enable the immune cells to destroy the invading pathogens. Simultaneously, the infected living cells as also the dead cells of the host need to be cleaned out, which activity is also triggered by the innate immune system, by a process called autophagy. Certain proteins known as adapter proteins are necessary for certain immune activation pathways. There are large numbers of adapter proteins in the body fluid, which form transitory complexes with other relevant proteins to activate the immune system in both innate and adaptive pathways. The adapter proteins can link multiple receptors sitting on the immune cells, and thereby activate different immune cells to effectively respond to microbial attacks. Adapter proteins have critical roles in the regulation of signal transduction, which functions are executed by the engagement of such proteins through surface receptors on multiple cell types. Several types of innate immune cells get activated by the actions of adapter proteins.[25]

Detection in humans through the innate immune pathways is achieved through germline-encoded pattern recognition receptors (PPR). PPR*s* are a series of innate immune receptors. The PPRs survey both extracellular as well as intracellular space for the conserved domain of the invading microbes through ligand- receptor-based mechanism. PPRs are classified to belong to five major families,[26] namely the Toll-like receptors (TLRs); C-type lectin receptors (CLRs);nucleotide-binding domain; leucine-rich repeat (LRR)-containing (or NOD-like) receptors(NLRs);RIG-I-like receptors (RLRs); and the AIM2-like receptors (ALRs). The outer membrane-bound cellular receptors are TLRs and CLRs while the other three are the intracellular receptors, residing inside the cells. The PRR-induced responses are both transcriptional as well as non-transcriptional.[27] Transcriptional responses include secretion of proinflammatory cytokines and interferons as well as other responses like autophagy responses through autophagic receptors, which trigger responses through host immune cells in both innate and adaptive pathways.[28,29]

The innate immune response is fast and more effective during the initial phase of attack by the pathogens. This response in particular in viral attacks shuts the viral load down to destruction by various mechanisms before it gets a chance to replicate. Even where some pathogens escape, the immune system gets time to activate the other responses. The innate immune response is taken over by the acquired immune system pathways by the CD4+ T cells in both Th-1 and Th-2 pathways. However, the activation of these pathways takes time ranging from a few days to about four weeks. Often the survival of the infected is determined within the first few days of infection. Consequently, if the innate immune system mounts an effective resistance to the pathogen during the initial phase, and keeps the invading microbes in considerable check, then the acquired immune response, which grows stronger over time after being activated, can tackle the disease reasonably well. Innate immune pathways are complex, and the full science of the pathways is yet evolving. It is reasonably clear that in innate immunity eventually the macrophages and neutrophils need to be activated to enable the body to more effectively defend against damages. Macrophages and neutrophils execute phagosome maturation (internalizing the pathogenic microbes within) and effectively coordinate as the bridge between innate and acquired immunity. The pH of the internal environment in phagosome is reduced to acidic pH, which serves as an environment for degradative enzyme activity. Further, the fusion of phagosome-lysosome in macrophages and neutrophils release the degradative enzymes and results in the elimination of intracellular pathogens. Probably through this ultimate reaction of the macrophages and neutrophils, the SARS-CoV-2 virus is cleared from the body of the infected host. However, it is not yet clear why every individual cannot mount the resistance equally effectively to get rid of the infecting virus.

## Innate immunity and mycobacterium infection

In a study in China, it was found that in COVID-19 patients, total T cells, CD4+ and CD8+ T cells were dramatically reduced,[30] especially in ICU patients, implicating thereby that such patients are less competent to fight the disease. In individuals suffering from Mtb, there is exhaustive loss[31] of T cells. It is therefore considered logical to conclude that if patients suffering from Mtb also get infected with SARS-CoV-2, the results are anticipated to be very adverse.

In multiple studies, it was found that a sizable number of patients dying from COVID-19 flu had one or more comorbid conditions. The Centers for Disease Control and Prevention (CDC), USA had reported that during the period from February 1, 2020, through August 22, 2020, of the deaths occurring in the USA from COVID-19 flu, 94% of the deceased had comorbid conditions.[32] Deaths due to COVID-19 flu during that period reported were 164,280 numbers. The comorbid factors included cardiovascular diseases. People aged 65y or older also died more in numbers. In another study[33] it was found that comorbid conditions such as hypertension, cardiovascular disease, and diabetes were the most common disease conditions in deaths occurring from COVID-19 flu. Other comorbid conditions in COVID-19 flu deaths were chronic kidney disease, malignancy, obesity, chronic pulmonary diseases, some other diseases, and increased age. Many COVID-19 flu deaths should also have included individuals suffering from Mtb or other mycobacterium infection, although deaths in patients in COVID-19 flu, also suffering from Mtb and other mycobacterium infection could not be found.

The author wishes to highlight that there is a difference between the individuals suffering from Mtb or other mycobacterium species, and those who were exposed to various mycobacterium species and have been able to clear the bacteria, thereby acquiring immunity to the disease. The author intends to suggest and ascertain if the sensitized immune system of the healthy individuals not suffering from tuberculosis is tutored to resist not only the subsequent attack from Mtb or other mycobacterium species but also to resist more efficiently from infection from SARS CoV-2. And if so, what could be a probable mechanism for this.

It is presently the prime thought that interferon (IFN)-gamma mediated memory responses of the CD 4+ T

cells represent the correlations of protection against tuberculosis (TB). A single infectious agent Mycobacterium tuberculosis (Mtb) represents about 90% of the cases who develop tuberculosis, although different kinds of other Mycobacterium species exist, which also cause the disease.[34-36] It has been observed that a percentage of individuals in close contact with active Mtb did not contract the disease. Usually, tuberculin skin test (TST) or *in vitro* based Interferon-γ (IFN-γ) release assays (IGRA) are considered to be the markers of immune conversion in response to Mtb exposure. It is considered that those who test persistently negative for these assays do not develop TB. It is also believed that individuals vaccinated with BCG are less prone to the risk of acquiring TB. The individuals resisting TB in household contact studies or community-based studies have been elaborately studied,[37] and interestingly no precise understanding has yet evolved about how individuals clear the infection immunologically.

It was earlier believed[38] that one-third of the global population had Mtb infection. This figure was revised later to one-fourth or even lower later.[39] However, only a small percentage of the infected is thought to be at risk of developing the disease because the infection is got rid of and Mtb eliminated by the action of an array of cytokines secreted by the immune system, particularly interferon-gamma by the CD4+ T cells. It was estimated that in 2011, there were 8.7 million incident cases of TB globally and about 1250 cases per one million population; further, in Asia, there were 59% of the cases followed by Africa (26%), the rest 15% cases were in other parts of the world.[40] The TB incidence came down in 2020 when estimated10 million people suffered from the disease of which 5.6 million were men, 3.3 million women, and 1.1 million children.[41] Here, the question is whether the rest of the population in Asia and Africa who were exposed to various mycobacterium species and could remain healthy from mycobacterium species were more competent to resist SARS-CoV-2 when compared with the population in countries that have less mycobacterium infection.

The author thinks that there is a difference between persistent exposure to Mtb and less persistent exposure. The immune system shall be activated even by one exposure although the extent of activation of the immune system may be less. It is important to ascertain how the complex immune system gets activated and remains in active state to prevent the exposed individuals from the active disease. It appears that there is a threshold limit of persistent exposure in a population that keeps most of the population disease-free from Mtb, although such subjects are exposed repeatedly. Such threshold limits may be in terms of the number and kinds of exposure of various kinds of tuberculosis species. There are speculations from such conjectures that natural innate immunity in some individuals and vaccination with BCG in others, resulting in imparting activation of the relevant immune cells to mount resistance against Mtb might be linked. The author speculates that innate immunity in individuals exposed to various kinds of mycobacterium species is elevated and tutored to face challenges from invasion by certain microbial species including SARS-CoV-2 viruses.

## DISCUSSION

When the presence of an infecting microbe is sensed by the immune system, the body fluid is charged with activities that correspond to innate responses by the innate leukocytes, which include the dendritic cells, natural killer cells, mast cells, eosinophils, and basophils besides the neutrophils and the macrophages. The full sequence of events in the innate responses is yet speculative although multiple sequential events are known. The start of the innate host defense response is, however, through pattern recognition receptors (PRRs) on the immune cells, which are present on the surface or within the cells. The response of the host defense is fast and occurs within minutes to hours of infection.

SARS -CoV-2 viruses spread through contact of droplets spread by sneezes, coughs, breathing, or even talking by an infected individual, who can transmit disease to non-infected individuals who come in contact with the infected. Even without touching, the physical closeness between infected and non-infected of less than a couple of feet promotes the spread, mainly through nasal and oral routes. SARS -CoV-2 is a single-stranded RNA virus.

Virus-infected cells are targeted for engulfment by macrophages and neutrophils in phagosomes, which get matured and the contents are digested and destroyed within the phagosomes. The antiviral innate immune mechanism is thought to be employed[42] to clear the virus-infected cells. In phagocytosis[43] particles bigger than 0.5 μm in size can be taken up by the phagocytic cells, while particles lesser than 0.5 μm are thought to be taken up by receptor-mediated endocytosis or pinocytosis. The Fc receptor-expressing immune effector cells can bind to the circulating antibody ligands in infection. Such Fc receptor-dependent antibody function of antibody-dependent cellular phagocytosis (ADCP) is a mechanism for clearance of virus and virus-infected cells.[44] In Mtb or other infective mycobacterium infection, protective responses such as the presence of memory B- cells and sensitized antibodies are present in

healthy hosts surviving such infection. Sensitized antibodies are the key components of the human adaptive immune system. Such antibodies may bind to the Fc receptor-expressing immune effector cells, activate the innate immune system through ADCP, and clear the SARS-CoV-2 virus fast.

Data provided in Table 2 shows that in 31 countries out of the 58, the deaths per one million populations were more than the global average of 782. More deaths can occur in COVID-19 infected individuals if such populations are also having one or more of the comorbid factors. Obesity, diabetes, cardiovascular diseases, high blood pressure, chronic obstructive pulmonary diseases (COPD), tuberculosis, and HIV among other microbial diseases, and higher proportions of the aged population (more than 65y), are identified as major morbidity conditions among others in various studies. To understand if increased deaths had occurred due to comorbid conditions, some insight was made country-wise, taking into consideration each factor related to comorbidity.

## Obesity

People with a Body Mass Index (BMI) of 30 and above are considered obese. Obesity triggers inflammation[45] in the body by the interaction between macrophages and adipocytes, and can lead to insulin resistance and diabetes. With progressive obesity, the resident macrophages mediate inflammation and insulin resistance.[46] It has been postulated[47] that increased expression of ACE2 in adipose tissues in obesity may increase the ease of SARS-CoV-2 infection and accessibility to this tissue, thereby firming up grounds for fast multiplication and the manifestation of the severity of the disease. World data on obesity rates[48,49] for most countries was higher where COVID-19 deaths were more; even in Peru, a comparatively poorer country, the% obese individuals were more than 15%.

## Diabetes

Diabetes mellitus (DM) is a characteristic familiar comorbid condition in individuals suffering from COVID-19 flu. In DM, the cure is also slow. Patients with DM suffering from COVID-19 flu are at higher risk of ICU admission and are found to be at higher mortality risks.[50,51] Patients with DM and other comorbid conditions like cardiovascular disease and hypertension were found to be more vulnerable to COVID-19 death.[33] Obesity in people is the most noteworthy risk factor for the development of diabetes. Over the years as obesity has increased globally so has been the increase in the incidence of diabetes.[52] The increased deaths from COVID-19 in different countries are thus correlated.

## Cardiovascular diseases and hypertension

In a study in the USA, it was found that during the initial phase of the COVID-19 pandemic, there was an increase in deaths caused by ischemic heart disease and hypertension giving the impression that COVID-19 flu may have had an indirect toll on patients with cardiovascular diseases.[53] The SARS-CoV-2 virus most frequently infects the lungs tissues first. But it can also infect the heart, vascular tissues, and circulating cells through angiotensin-converting enzyme 2(ACE-2) receptors. In several infected patients, acute cardiac injury is observed, which is implicated with chronic consequences including fatality.[54] In a study it was observed that the availability of adequate materials for treating cardiovascular diseases during the pandemic was not available; the supply line could not cope with the increased demand situation, and this led to large mortality, a situation which needs to be kept in mind.[55] Infection from SARS-Co V-2 often leads to anxiety, stress, and depression, which behavioral changes could significantly increase blood pressure (BP). Increases in BPare likely to adversely affect individuals suffering from respiratory or cardiovascular diseases. In a study in the USA the health data from more than half a million US citizens from 50 states and the District of Columbia, it was found[56] that there was a rise in average blood pressure during the early peak of the pandemic. If high BP is left uncontrolled, then this can lead to an increased risk for strokes, heart attacks, kidney disease, and other health problems.[57] It is thus the impression that both cardiovascular diseases and hypertension have contributed to increased mortality from COVID-19 infected patients.

## Chronic obstructive pulmonary diseases, tuberculosis, and COVID-19 deaths

People with COPD, having damaged and weakened lungs are thought to be at higher risk of respiratory disease, which includes SARS-CoV-2 viral infection.[58] In a Korean study, it was revealed that COPD is associated with increased risk for COVID-19. However, having COPD was not thought to confer substantial risk for severe COVID-19 and mortality.[59] In general, COPD is known to cause substantial global morbidity and mortality. Tuberculosis is strongly associated with the presence of COPD in adults though the contribution of pulmonary tuberculosis to the set of causes of COPD is often missed out.[60] Active TB should be taken into consideration when dealing with efforts to contain the infection from SARS-Co V-2.

Infection from mycobacterium species and recovery may impart a stronger defense to COVID-19 flu. To examine if there is any linkage between the two, the data on COVID-19 death per one million in different countries

**Table 3: Incidence of the intensity of tuberculosis and COVID-19 death per one million population**

| Serial No | Name of the country | Incidence of tuberculosis: The year 2020(50 per hundred thousand or above) | SARS-CoV-2 deaths as of March 19, 2020, per one million population |
|---|---|---|---|
| 1 | Hong Kong | 56.0 | 711 |
| 2 | China | 59.0 | 3 |
| 3 | Kazakhstan | 69.0 | 713 |
| 4 | Georgia | 70.0 | 4186 |
| 5 | Ukraine | 73.0 | 2483 |
| 6 | Peru | 116.0 | 6273 |
| 7 | Thailand | 150.0 | 345 |
| 8 | Vietnam | 176.0 | 422 |
| 9 | India | 188.0 | 368 |
| 10 | Bangladesh | 218.0 | 174 |
| 11 | Pakistan | 259.0 | 133 |
| 12 | Indonesia | 301.0 | 551 |
| 13 | South Africa | 554.0 | 1648 |

along with the incidence of tuberculosis were compared. Table 3 provides the details.

It is seen from the above table that in populated countries where the incidence of tuberculosis was 50 per hundred thousand or more, there the incidence of death from COVID-19 flu was 1000 numbers or less per one million population.

In two countries namely China and Hong Kong, the deaths per one million population were low, being 3 and 711 respectively. In China, perhaps strict rules of reporting, mass testing and stern rules of isolation of infected on doubts, extending considerable medical care to the infected, vaccination of every deserving recipient by the authorities, maintaining emergency supply lines of food and medicine to the citizens during the pandemic, adherence of uncompromising rules of national discipline among the citizens may have been the causes for such unprecedented decreased deaths. In Hong Kong perhaps the preponderance of tuberculosis sensitized healthy population besides other preventive factors may have been the cause for lower deaths.

In four countries namely Georgia, Ukraine, Peru, and South Africa, this was not the case, however. In African countries, the incidence of COVID-19 flu was less than in other parts of the world. While constructing Table 1, the cut-off total infection from SARS-Co V-2 virus as of March 19, 2022, included in the Table was one million infected cases, and only two African countries, namely South Africa and Tunisia got included. In Tunisia, the incidence of tuberculosis is low (36 per one hundred thousand population in 2020), and therefore SARS-CoV-2 deaths are anticipated to be high, which is the case (2333 deaths per one million population, as of March 19, 2020). In South Africa, the high incidence of COVID-19 deaths despite high tuberculosis incidence seems to be due to more deaths from comorbid cases. Individuals infected with SARS-Co V-2 having active tuberculosis as also tuberculosis and HIV infection together are considered highly vulnerable; more deaths may have occurred in these comorbid patients, and the figures of deaths may have been majorly contributed from this cohort. It was not possible to ascertain what was the quantum of a healthy population that was sensitized to mycobacterium infection but got rid of the disease. It is this population that is being referred to, who are thought to be more resistant to SARS-Co V-2through innate immunity pathways. Moreover, dominance in delta and beta variants led to increased infection and the overburdened health services were inadequate for treating the infected adequately. Most countries in the African continent have a high incidence of tuberculosis (more than 50 cases per hundred thousand populations in 2020),[61] and therefore the number of healthy populations sensitized from mycobacterium infection may have been more in this part of the world. This factor may have contributed to a great extent to lesser deaths in Africa besides other factors.

The COVID-19 epidemiology data of African countries were analyzed. As of 31st December 2020, the SARS-Co V-2 infection in African countries constituted 3.4% of the numbers infected globally, and the death reported was 3.6% of all reported global deaths from this infection.[62] The precise causes of lower infection in Africa were not determined. However, these data tend to support the conjecture that Africa was not highly vulnerable to the disease. In another study, factors such as younger age population, adequate vitamin D status in blood as a result of exposure to sunlight by the population, generation of cross-immunity from other viruses, and lessons learned earlier from other infectious diseases such as HIV and Ebola, thereby getting more experienced and more capacitated to deal with infectious diseases, have been considered to be causes for lower infection in the continent. Also included

were the reasons for the low testing rate, resulting in lower determination of the causes of diseases.[63]

In other three countries namely Georgia, Ukraine, and Peru despite the high incidence of tuberculosis, deaths per one million population were also high. It is presumed that while there was sizable mycobacterium tuberculosis sensitized healthy population in these three countries (as the Mtb-infected population was high), there were other kinds of the vulnerable population such as more numbers of aged people (especially in Georgia and Ukraine), populations with increased body-mass index, cardiovascular diseases, high blood pressure, and diabetes among others, which factors led to higher deaths. There may not have been adequate vaccination, and the medical infrastructure may have been inadequate and fatigued, causing the increase in deaths.

In the other nine countries in Table 3, there appears to be a correlation between and among the incidence of tuberculosis and COVID-19 deaths. The author hypothesizes that in tuberculosis-prone countries, there is a sizable portion of the tuberculosis-sensitized population who are healthy and have defeated the disease, thereby acquiring more sensitized innate immune cells which are competent to resist SARS-CoV-2. It is believed that BCG vaccinated individuals resist SARS-Co-V-2 infection more proficiently,[63] which is consistent with the above hypothesis. The exact mechanism of activation of innate immune cells needs to be ascertained in future research work.

## Aging

Aging is thought to be a multifaceted cellular process, involving a great number of molecular and cellular mechanisms in different organs and tissues of the human body. Alterations take place in both innate and adaptive immune cells in age. In adaptive immunity, where T cells recognize and kill a countless number of pathogen-infected or defective cells using a diverse set of T cell receptors (TCRs), it had been shown[64] that the affinity of TCR to cognate antigens goes down substantially with age. The integrity and intensity of innate immunity manifestation essentially through pattern recognition receptors (PPR) by the macrophages and monocytes may also be coming down. Consequently, in a study on adults of 65y and longer, it was found[65] that in such age group, on contacting COVID-19 flu, a large percentage of such infected were to be hospitalized for treatment, and they had a 23-fold greater risk of death than those under 65y. The percentage of the aged population (65y and longer) in countries registering higher deaths per one million population was generally much higher than the countries where such deaths were lower. For example, in almost all countries where deaths per one million population were1000 and above and where the population of 65 y and above was 15% and above(of the total population), in those countries the intensity of deaths was quite high [Table 2 for reference]. There were exceptions to such observations in a few countries only such as Japan, South Korea, Norway, Hong Kong, Denmark, and Canada. In these countries perhaps more effective protective measures were established such as fast vaccination, maintenance of safe distance among people, frequent washing of hands, etc, and perhaps the health infrastructure in these countries was also comparatively better. It is quite clear from the information in Table 2 that more effective intervention is necessary to protect the aged individuals when there is a pandemic.

In a study,[66] the case fatality rate (CFR) in different countries was thought to be linked to temporal and special factors. The values of disability-adjusted life years (DALYs) were thought to be associated with temporal changes, and deaths in such countries were attributed to comorbid conditions in COVID-19 infected patients such as cardiovascular diseases, cancer, and chronic respiratory diseases. Certain demographic, economic, and political variables such as increased share of the population of age 70y and above, smoking habits, GDP per capita, and level of democracy were thought to be linked with increased deaths. The investigators did not study the most populated countries like India, and China as also many other poor Asian and African countries, where the above-cited correlations could not be found by the author and did not show such a relationship with COVID-19 deaths.

## Vaccines based on attenuated virus

All the approved vaccines were effective in considerably protecting the recipients and mounting resistance to the spread of the disease. Some kinds and types of vaccines were more effective than others. There was no vaccine, however, which imparted 100% protection. As the SARS-Co V-2 virus mutates, there is wisdom to design vaccines that target the fixed parts of the genome of the virus. This implies that proteins translated by the fixed parts of the genome need to be considered as antigens for designing vaccines; such vaccines are anticipated to be more universal. However, if the immune system does not produce adequate quantities of neutralizing antibodies against such proteins then such vaccines would not be useful. This point requires to be kept in mind while developing and selecting attenuated viral strains. The use of multiple numbers of attenuated strains could be thought of. At present, there is no approved SARS-Co V-2 vaccine based on using an attenuated strain. Such vaccines, when developed are anticipated to produce neutralizing antibodies for a longer time in the recipients,

being a live virus, and might provide protection more effectively from multiple wide ranges of variants.

## CONCLUDING REMARKS

Mass vaccination of the population of all ages above adulthood seems to be the most effective strategy to protect people during the COVID-19 pandemic. The aged population above 65 y is more vulnerable and needs to be protected fast through vaccination. Certain major morbidity conditions among others identified are obesity, diabetes, cardiovascular diseases, high blood pressure, chronic obstructive pulmonary diseases (COPD), tuberculosis, and HIV among other microbial diseases, and higher proportions of the aged population (more than 65y), are identified as major conditions among others, contributing to increased deaths. National policies need to be made and implemented to minimize the morbidity conditions, and to ensure adequate medical protection of their population, especially the aged population, 65y and above. Inclusion of a suitable inactivated multivalent human influenza vaccine in the National Programs along with approved SARS-CoV-2 vaccines is anticipated to be more beneficial to protect the target population from the pandemic.

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There are no conflicts of interest.

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