Journal of Vaccines, Immunology and Immunopathology
Pathak S and Nandi D. J Vaccines Immunol 8: 196.
www.doi.org/10.29011/2575-789X.000196
www.gavinpublishers.com

Research Article

Lower Incidences and Deaths Due to COVID-19 in Countries with high Deaths Due to Tuberculosis and Flu: a 2021-2022 Update

Sanmoy Pathak, Dipankar Nandi*

Department of Biochemistry, Indian Institute of Science, Bangalore-560012, India

***Corresponding author:** Dipankar Nandi, Department of Biochemistry, New Biological Sciences, Indian Institute of Science, Bangalore-560012, India

Citation: Pathak S, Nandi D (2023) Lower Incidences and Deaths Due to COVID-19 in Countries with high Deaths Due to Tuberculosis and Flu: a 2021-2022 Update. J Vaccines Immunol 8: 196. DOI: 10.29011/2575-789X.000196

Received Date: 22 June, 2023; **Accepted Date:** 26 June, 2023; **Published Date:** 28 June, 2023

Abstract

Heterogeneity in number of deaths in various countries due to COVID-19 is likely due to multiple factors. Previously, our laboratory has shown, using 2020 epidemiological data, that countries with high deaths due to tuberculosis and flu display less COVID-19 deaths. Also, countries with high BCG but low flu vaccinations display less COVID-19 deaths. It was important to address whether this trend held as the pandemic progressed in 2021-2022 given the rise of SARS-CoV2 variants and COVID-19 vaccinations. In this study, countries with more than 10,000 COVID-19 deaths were selected at four time points and the data was analysed. COVID-19 incidences/million and deaths/million were obtained from various data bases and correlation analysis was performed with tuberculosis deaths, flu deaths, BCG and flu vaccination coverages. The main findings are: First, countries with high tuberculosis deaths show negative correlation with COVID-19 incidences and deaths. This pattern is also true for countries with high BCG vaccinations. Second, countries with high flu deaths display less COVID-19 incidences and deaths. Concomitantly, countries with high flu vaccinations show higher COVID-19 incidences and deaths. Third, countries with high deaths due to tuberculosis and flu display lower COVID-19 incidences and deaths. Finally, countries with high BCG coverage and tuberculosis deaths (e.g. Bangladesh, India, Indonesia, etc) display lower COVID-19 incidences and deaths, compared to countries with high BCG coverage but low tuberculosis deaths (e.g. Brazil, Mexico, Russia etc), demonstrating roles for both. This global study reveals a complex interplay of the roles of other respiratory pathogens in limiting COVID-19.

Keywords: BCG; COVID-19; Flu; Tuberculosis; Vaccinations

Introduction

COVID-19 is a disease that is caused by SARS-COV2, a single stranded positive RNA virus. It is responsible for the recent pandemic leading to widespread deaths and disruption in lives and economies of nations. SARS-CoV2 infects the respiratory tract causing mild symptoms or, in severe cases, causes damage to the lungs [1]. The SARS family of viruses have a similar mechanism of entry in host cells using multiple mechanisms. The spike glycoprotein present in the virus plays important roles and interacts with the receptor angiotensin converting enzyme (ACE)2 on host cells. In addition, several other viral as well as host proteins such as cellular transmembrane proteases (e.g TMPRSS2), furin proteases etc are involved in aiding the replication of SARS-CoV2 viral particles [2]. A better understating of the viral replication cycle will be the key to the development of inhibitors some of which are likely to act as drugs.

The economic damage and loss of lives due to COVID-19 has been immense with official world- wide deaths in the range of 1.88 million in 2020, 3.58 million in 2021 and 1.22 million in 2022. Mortality due to COVID-19 is variable across different countries and there may be several reasons for this heterogeneity: population age, sex, temperature, cultural norms such as the use of masks, better health care infrastructure, comorbidities such as hypertension, obesity, etc [3-5]. Recent studies have demonstrated the critical roles of host derived autoimmune antibodies to Interferons, polymorphisms in Toll-like receptors in protection against SARS-CoV2 infections [6]. Additionally, prior exposure to infectious pathogens may boost cross-reactive immunity to pathogens. For example, *H. pylori* infections may lower tuberculosis incidences [7]. Also, pre-existing infections with HIV or tuberculosis can also lead to COVID-19 severity [8]. On the other hand, malaria incidences are known to lower COVID-19 [9]. It is well known that previous exposure to family members of coronaviruses that cause common cold leads to better T cell immunity against SARS-Cov2 [10]. Another important aspect is vaccinations, which are an established public safety shield as well as a highly cost-effective strategy. They are a key factor in enhancing immunity against a vast number of pathogens, especially in protecting children [11,12]. Interestingly, immunizations with oral polio vaccine, measles vaccine, hepatitis vaccine [13-15] are known to reduce COVID-19 cases and these are likely due to boost non-specific immunity, resulting in heterologous protection.

The vast differences in the number of COVID-19 deaths in various countries led us to investigate the correlation between COVID-19 incidences or deaths with the prevalence of various diseases using data available in the public domain. Previously, we had shown that countries with high amounts of deaths due to flu or tuberculosis display less COVID-19 deaths in 2020 [16]. Also, countries with high amounts of flu vaccination led to higher COVID-19 deaths. On the other hand, countries with high BCG vaccine coverage led to lower COVID-19 deaths [16]. An important question to address is whether this trend was observed as the pandemic spread in 2021 and 2022. This aspect is important as there was a rise in variants as well as an increase in vaccinations. We find that the trends observed initially in 2020 are sustained and even better now in 2021-2022 as COVID-19 incidences as well as deaths correlate well with time. The implications of our findings are discussed in detail in this study.

Methods

Study design

Countries with more than 10,000 COVID-19 deaths were selected at four time points and the data was analysed: 24th May 2021, 31st December 2021, 14th April 2022 and 31st December 2022.

Selection of Samples

A set of 62 countries were selected on the criteria of deaths that are more than 10,000 by 14th April 2022 (Figure 1). These countries were arranged and tables were constructed where COVID-19 incidences/million and deaths/million were obtained from: https://www.worldometers.info/coronavirus/ and https://ourworldindata.org/coronavirus#explore-the-global-situation. These factors were initially correlated with pathogen exposure. TB deaths/100,000 and Flu deaths/100,000 and this data was obtained from: https://www.worldlifeexpectancy.com/world-health-rankings. Next, correlation analysis was performed with different vaccination programs. BCG coverage for different countries were obtained from http://www.bcgatlas.org/. BCG Atlas uses three distinct methods of obtaining data: First, it uses a questionnaire method which is sent to at least two individuals in each country based on their expertise on TB research, TB control programs and public health/vaccination programs. It includes data regarding any changes that have occurred in the last 25 years. It also includes criteria such as tuberculin skin testing, effect of HIV and different vaccine strains playing a role in affecting extent of TB infection. Secondly, case reports, published papers and policy documents from the government are also included as a part of the overall database. Finally, it uses the immunization data from the World Health Organization Vaccine Preventable Diseases Monitoring System as mentioned in http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleSelect.cfm [17]. Flu vaccination coverage data was obtained from various sources: https://www.statista.com/chart/16575/global-flu-immunization-rates-vary/, https://www.oecd.org/health/graph-of-the-month.htm and published manuscripts [18-20]. The COVID-19 vaccination coverage in each country was extracted from: https://ourworldindata.org/covid-vaccinations. These factors were compared to COVID-19 deaths/million and incidences/million at the four time points.

COVID variant kinetics data was obtained from: https://covariants.org/variants which helped to confirm the dominant COVID-19 strains responsible for infection and deaths in each country at mentioned time points. The early 2020 time points suggested that a dominant strain wasn't identified and was therefore labelled as "others" (Table 1).

Countries	Dominant variant (17th May2020)	Dominant variant (1st October 2020)	Dominant variant (31st Dec 2020)	Dominant variant (24th May 2021)	Dominant variant (31st December 2021)	Dominant variant (14th April 2022)	Dominant variant (31st December 2022|)
USA	others	others	others	Alpha, V1 (20 I)	Omicron (21K)	Omicron (21L)	Omicron (22E)
Brazil	others	others	others	Gamma, V3 (20J)	Omicron (21K)	Omicron (21L)	Omicron (22E)
India	others	20E (EU1)	20E (EU1)	Delta (21J)	Omicron (21L)	Omicron (21L)	Omicron (22F)
Russia	others	others	others	Delta (21J)	Omicron (21K)	Omicron (21L)	Omicron (22F)
Mexico	others	others	others	Gamma, V3 (20J)	Omicron (21K)	Omicron (21L)	Omicron (22E)
Peru	others	others	others	Lamda (21G)	Omicron (21K)	Omicron (21L)	Omicron (22F)
UK	others	others	Alpha, V1 (20 I)	Delta (21J)	Omicron (21K)	Omicron (21L)	Omicron (22E)
Italy	others	others	others	Alpha, V1 (20 I)	Omicron (21K)	Omicron (21L)	Omicron (22E)
Indonesia	others	others	others	others	Omicron (21K)	Omicron (21L)	Omicron (22F)
France	others	20 A.EU2	20 A.EU2	Alpha, V1 (20 I)	Omicron (21K)	Omicron (21L)	Omicron (22E)

Table 1: Dominant COVID-19 variants in countries with high COVID-19 deaths from 17th May 2020-31st December 2022.

Statistical Analysis

Correlation analysis was performed by using Spearman's correlation analysis and the Spearman's correlation coefficient (R_s) and p values were calculated using a Spearman's correlation calculator: https://www.socscistatistics.com/tests/spearman/default2.aspx. Correlation was considered significant if $p<0.1$. Bar graphs were constructed for countries grouped either by using extent of TB and Flu deaths or using BCG and Flu vaccination coverages. Statistical analysis was done using One way ANOVA to calculate the statistical significance. Statistical analysis was considered significant if $p<0.1$.

Results

To perform the epidemiological study, a subset of 62 countries were selected based on the criteria in which the total deaths due to COVID-19 were greater than 10000 by 14th April 2022. To evaluate changes with time, the cluster of countries were arranged on the basis of four distinct time points (Table 2-5): 24th May 2021, 31st December 2021, 14th April 2022 and 31st December 2022 and compared to four conditions (Figure 1): Flu deaths/100,000, TB deaths/100,000, Flu vaccination coverage and BCG coverage.

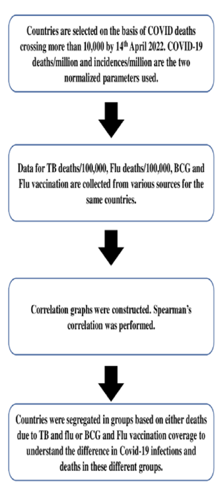

Figure 1: Flow chart describing the methodology used to perform the mentioned epidemiological study.

Country	COVID-19 deaths/million	COVID-19 incidences/million	BCG coverage (%)	Flu Vac coverage (%)	TB deaths/100,000	Flu deaths/100,000
USA	1739.44	98321.53	0	69.1	0.09	8.86
Brazil	2100.77	74919.89	86.9	71.8	2.19	38.59
India	218.27	19015.94	99	0	32.84	35.3
Russia	805.03	34222.23	99	0	4.61	15.22
Mexico	1749.69	18801.8	95	82.3	1.58	19.44
Peru	5363.06	56543.68	80	89	7.14	44.2
UK	2290.66	66137.91	75	70.5	0.25	20.37
Italy	2115.70	71051.01	0	50	0.2	6.3
Indonesia	180.66	6465.04	92.2	0	34.32	25.49
France	1611.85	83286.13	0	50	0.23	8.06
Iran	896.78	32111.85	99.5	0	1.25	16
Colombia	1653.97	62640.85	90	20	2.37	19.35
Germany	1048.13	43800.49	0	34.8	0.15	7.66
Argentina	1644.99	78270.92	95	0	1.29	60.51
Poland	1904.18	71911.35	93.7	13.4	1	22.64
Spain	1678.59	76695.23	0	51.4	0.22	7.96
South Africa	940.76	27345.83	90.5	0	39.83	83.23
Turkey	547.87	60861.66	94	5.9	0.35	14.42
Romania	1550.92	54720.9	90.15	15	3.59	26.33
Phillippines	175.47	10251.96	99	60	26.98	146.92
Chile	1464.51	68112.58	97.8	75	1.54	12.46
Hungary	3044.35	80497.8	99	30	0.38	7.19
Vietnam	0.45	55.04	96	0	9.33	25.84
Czechia	2856.89	158003.96	80	20	0.13	16.64
Canada	662.09	35580.49	0	60	0.13	7.69
Bulgaria	2543.32	61446.44	96	0	0.95	10.7
Ecuador	1135.54	23287.48	0	0	3.49	28.8
Malaysia	68.77	15280.71	99	0	3.87	90.22
Belgium	2140.39	90067.68	0	60	0.18	14.69
Pakistan	88.16	3841.21	95	0	23.21	37.37
Japan	99.55	5824.6	98	51	0.53	16.56
Bangladesh	73.22	4617.9	99	0	25.88	22.96
Greece	1131.79	37667.99	31	55	0.25	18.43
Tunisia	1000.82	27226.52	92	0	1.15	15.33
Thailand	11.26	1844.05	99	0	9.62	29.71
Iraq	372.45	26340.32	99	0	2.26	15.14
Egypt	135.14	2297.36	99	0	0.54	25.25
Netherlands	1004.53	93016.86	0	80	0.07	9.84
Portugal	1653.82	82316.89	99	52	0.83	18.35
Bolivia	1156.09	28603.54	99	30	10.73	69.51
South Korea	37.39	2643.65	98	85.1	1.93	25.21
Slovakia	2257.13	136256.07	90	12	0.3	20.2
Myanmar	59.78	2644.22	91	0	38.12	40.28
Paraguay	1264.06	49506.51	99	85	4.51	27.39
Sweden	1372.49	100322.87	26.4	55	0.09	8.29
Guatemala	454.84	13878.34	55	0	2.31	70.32
Austria	1439.91	71203.05	99	20	0.21	5.8
Georgia	1234.44	90258.08	99	0	3.9	13.89
Sri Lanka	57.09	7657.15	96	0	3.45	13.67
Morocco	246.14	13805.15	99	0	8.35	22.11
Serbia	987.84	103370.46	99	10	0.63	10.5
Croatia	1952.89	87848.21	98	30	0.65	8.4
Bosnia and Herzegovina	2797.36	62900.61	95	0	1.6	7.26
Jordan	841.74	64809.86	86	0	0.13	15.14
Switzerland	1229.72	78640.27	0	45	0.1	6.97
Kazakhstan	372.41	22233.63	99	0	1.56	18.79
Nepal	217.45	17037.71	96	0	72.19	29.37
Moldova	1985.95	77831.21	99	0	3.79	21.42
Honduras	602.04	22344.4	99	70	6.16	17.65
Israel	689.48	88831.3	90	59.8	0.14	9.67
Lebanon	1373.95	98122.61	0	0	1.02	14.8

Table 2: List of countries with COVID-19 deaths/million and COVID-19 incidences/million, BCG, Flu Vac coverage, TB and Flu deaths/100,000 on 24th May 2021.

Country	COVID-19 deaths/million	COVID-19 incidences/million	BCG coverage (%)	Flu Vac coverage (%)	TB deaths/100,000	Flu deaths/100,000
USA	2,447.72	162300.44	0	69.1	0.09	8.86
Brazil	2,889.28	103532.01	86.9	71.8	2.19	38.59
India	341.78	24599.38	99	0	32.84	35.3
Russia	2,079.84	71316.21	99	0	4.61	15.22
Mexico	2,360.85	31212.51	95	82.3	1.58	19.44
Peru	6,010.68	67455.47	80	89	7.14	44.2
UK	2,632.72	191647.01	75	70.5	0.25	20.37
Italy	2,316.78	103759.24	0	50	0.2	6.3
Indonesia	526.34	15472.59	92.2	0	34.32	25.49
France	1,833.47	147730.1	0	50	0.23	8.06
Iran	1,496.44	69953.26	99.5	0	1.25	16
Colombia	2,521.54	99422.39	90	20	2.37	19.35
Germany	1,338.02	85767.49	0	34.8	0.15	7.66
Argentina	2,587.33	124244.51	95	0	1.29	60.51
Poland	2,516.86	103073.49	93.7	13.4	1	22.64
Spain	1,882.73	132357.57	0	51.4	0.22	7.96
South Africa	1,533.21	57740.22	90.5	0	39.83	83.23
Turkey	969.6	111113.33	94	5.9	0.35	14.42
Romania	3,037.68	92012.11	90.15	15	3.59	26.33
Phillippines	451.11	24610.62	99	60	26.98	146.92
Chile	2,005.62	92150.5	97.8	75	1.54	12.46
Hungary	4,027.28	126053.65	99	30	0.38	7.19
Vietnam	330.04	17632.27	96	0	9.33	25.84
Czechia	3,430.87	235918.75	80	20	0.13	16.64
Canada	793.63	57827.95	0	60	0.13	7.69
Bulgaria	4,486.00	110161.16	96	0	0.95	10.7
Ecuador	1,891.93	30521.52	0	0	3.49	28.8
Malaysia	937.1	81267.85	99	0	3.87	90.22
Belgium	2,437.95	180624.31	0	60	0.18	14.69
Pakistan	125.01	5495.32	95	0	23.21	37.37
Japan	147.57	13983.73	98	51	0.53	16.56
Bangladesh	165.75	9262.06	99	0	25.88	22.96
Greece	1,982.51	116596.65	31	55	0.25	18.43
Tunisia	2,084.00	58813.46	92	0	1.15	15.33
Thailand	302.68	31011.54	99	0	9.62	29.71
Iraq	554.84	47054.44	99	0	2.26	15.14
Egypt	198.85	3473.96	99	0	0.54	25.25
Netherlands	1,198.00	179543.86	0	80	0.07	9.84
Portugal	1,840.31	135299.91	99	52	0.83	18.35
Bolivia	1,626.73	49063.11	99	30	10.73	69.51
South Korea	107.33	12259.83	98	85.1	1.93	25.21
Slovakia	3,046.83	242950.82	90	12	0.3	20.2
Myanmar	358.1	9797.73	91	0	38.12	40.28
Paraguay	2,479.79	68738.91	99	85	4.51	27.39
Sweden	1,462.68	124631.77	26.4	55	0.09	8.29
Guatemala	914.67	35214.19	55	0	2.31	70.32
Austria	1,882.86	142154.97	99	20	0.21	5.8
Georgia	3,661.01	249638.06	99	0	3.9	13.89
Sri Lanka	687.17	26898.17	96	0	3.45	13.67
Morocco	400.36	25711.27	99	0	8.35	22.11
Serbia	1,846.45	189089.73	99	10	0.63	10.5
Croatia	3,076.99	177464.25	98	30	0.65	8.4
Bosnia and Herzegovina	4,105.24	90091.32	95	0	1.6	7.26
Jordan	1,132.01	94224.42	86	0	0.13	15.14
Switzerland	1,404.38	152464.9	0	45	0.1	6.97
Kazakhstan	948.66	55290.14	99	0	1.56	18.79
Nepal	385.88	27119.36	96	0	72.19	29.37
Moldova	3,165.11	114926.92	99	0	3.79	21.42
Honduras	1,015.05	36366.07	99	70	6.16	17.65
Israel	887.2	146463.33	90	59.8	0.14	9.67
Lebanon	1,627.50	132598.17	0	0	1.02	14.8

Table 3: List of countries with COVID-19 deaths/million and COVID-19 incidences/million, BCG, Flu Vac coverage, TB and Flu deaths/100,000 on 31st December 2021.

Country	COVID-19 deaths/million	COVID-19 incidences/million	BCG coverage (%)	Flu Vac coverage (%)	TB deaths/100,000	Flu deaths/100,000	Covid vaccine coverage
USA	3042	238692.15	0	69.1	0.09	8.86	65.98
Brazil	3078	140480.28	86.9	71.8	2.19	38.59	76.28
India	372	30370.99	99	0	32.84	35.3	60.75
Russia	2565	122934.17	99	0	4.61	15.22	50.22
Mexico	2467	44904.24	95	82.3	1.58	19.44	61.37
Peru	6294	104396.83	80	89	7.14	44.2	78.94
UK	2525	322144.58	75	70.5	0.25	20.37	72.79
Italy	2691	264159.38	0	50	0.2	6.3	79.33
Indonesia	560	21918.82	92.2	0	34.32	25.49	59.11
France	2210	407393.54	0	50	0.23	8.06	77.89
Iran	1640	81355.2	99.5	0	1.25	16	67.53
Colombia	2695	117387.86	90	20	2.37	19.35	68.73
Germany	1594	280399.71	0	34.8	0.15	7.66	75.42
Argentina	2794	199074.48	95	0	1.29	60.51	81.47
Poland	3069	150132.78	93.7	13.4	1	22.64	59.29
Spain	2217	245217.61	0	51.4	0.22	7.96	86.32
South Africa	1653	62430.28	90.5	0	39.83	83.23	30.31
Turkey	1147	175619.45	94	5.9	0.35	14.42	62.35
Romania	3442	146509.81	90.15	15	3.59	26.33	27.91
Phillippines	53	31867.9	99	60	26.98	146.92	33.64
Chile	2953	179855.77	97.8	75	1.54	12.46	90.79
Hungary	4789	188564.53	99	30	0.38	7.19	64.26
Vietnam	435	105864.81	96	0	9.33	25.84	79.2
Czechia	3728	369788.42	80	20	0.13	16.64	64.02
Canada	1009	94327.12	0	60	0.13	7.69	82.09
Bulgaria	5374	169415.9	96	0	0.95	10.7	15.76
Ecuador	1960	48085.38	0	0	3.49	28.8	77.48
Malaysia	1071	128842.87	99	0	3.87	90.22	80.6
Belgium	2681	340853.57	0	60	0.18	14.69	78.54
Pakistan	133	6475.78	95	0	23.21	37.37	53.75
Japan	232	58857.92	98	51	0.53	16.56	80.33
Bangladesh	179	11404.09	99	0	25.88	22.96	69.64
Greece	2788	310494.72	31	55	0.25	18.43	73.41
Tunisia	2370	84061.04	92	0	1.15	15.33	53.24
Thailand	393	55696.76	99	0	9.62	29.71	72.42
Iraq	602	52205.4	99	0	2.26	15.14	17.78
Egypt	233	4612.82	99	0	0.54	25.25	32.08
Netherlands	1291	456928.2	0	80	0.07	9.84	72.22
Portugal	2168	377898.94	99	52	0.83	18.35	92.6
Bolivia	1832	73933.87	99	30	10.73	69.51	49.31
South Korea	426	312891.98	98	85.1	1.93	25.21	86.8
Slovakia	3627	443864.8	90	12	0.3	20.2	50.74
Myanmar	353	11305.55	91	0	38.12	40.28	41.02
Paraguay	2577	95630.49	99	85	4.51	27.39	47.74
Sweden	1827	236601.9	26.4	55	0.09	8.29	75.08
Guatemala	944	46927.88	55	0	2.31	70.32	33.27
Austria	1875	454766.46	99	20	0.21	5.8	73.03
Georgia	4225	441382.76	99	0	3.9	13.89	31.72
Sri Lanka	765	30358.62	96	0	3.45	13.67	67.16
Morocco	426	31082.73	99	0	8.35	22.11	62.59
Serbia	1838	290272.77	99	10	0.63	10.5	97.58
Croatia	3885	276027.63	98	30	0.65	8.4	54.9
Bosnia and Herzegovina	4857	116416.73	95	0	1.6	7.26	25.93
Jordan	1353	150183.92	86	0	0.13	15.14	43.59
Switzerland	1576	408286.46	0	45	0.1	6.97	68.77
Kazakhstan	712	71872.88	99	0	1.56	18.79	48.56
Nepal	397	32036.84	96	0	72.19	29.37	65.44
Moldova	2860	157703.97	99	0	3.79	21.42	13.14
Honduras	1069	40378.96	99	70	6.16	17.65	48.05
Israel	1143	426070.8	90	59.8	0.14	9.67	66.02
Lebanon	1532	199536.81	0	0	1.02	14.8	32.72

Table 4: List of countries with COVID-19 deaths/million and COVID-19 incidences/million, BCG, Flu Vac coverage, TB deaths/100,000, Flu deaths/100,000 and COVID vaccination on 14th April 2022.

Country	COVID-19 Deaths/million	COVID-19 incidences/million	BCG coverage (%)	Flu Vac coverage (%)	TB deaths/100,000	Flu deaths/100,000
USA	3,231.11	297915.91	0	69.1	0.09	8.86
Brazil	3,222.52	168736.66	86.9	71.8	2.19	38.59
India	374.48	31527.46	99	0	32.84	35.3
Russia	2,665.89	148504.06	99	0	4.61	15.22
Mexico	2,596.77	56739.08	95	82.3	1.58	19.44
Peru	6,409.24	130945.58	80	89	7.14	44.2
UK	3,197.58	357509.47	75	70.5	0.25	20.37
Italy	3,127.54	425894	0	50	0.2	6.3
Indonesia	582.98	24391.22	92.2	0	34.32	25.49
France	2,389.38	580037.35	0	50	0.23	8.06
Iran	1,633.92	85387.82	99.5	0	1.25	16
Colombia	2,735.11	122154.77	90	20	2.37	19.35
Germany	1,936.73	448242.03	0	34.8	0.15	7.66
Argentina	2,859.22	217338.36	95	0	1.29	60.51
Poland	2,973.95	159782.62	93.7	13.4	1	22.64
Spain	2,462.12	287734.47	0	51.4	0.22	7.96
South Africa	1,712.49	67606.27	90.5	0	39.83	83.23
Turkey	1,185.86	198258.62	94	5.9	0.35	14.42
Romania	3,427.09	168291.09	90.15	15	3.59	26.33
Phillippines	565.82	35172.01	99	60	26.98	146.92
Chile	3,222.45	256967.7	97.8	75	1.54	12.46
Hungary	4,865.41	219298.62	99	30	0.38	7.19
Vietnam	439.83	117380.59	96	0	9.33	25.84
Czechia	4,014.77	436428.38	80	20	0.13	16.64
Canada	1,280.43	117155.65	0	60	0.13	7.69
Bulgaria	5,619.03	190520.88	96	0	0.95	10.7
Ecuador	1,996.56	57800.28	0	0	3.49	28.8
Malaysia	1,085.88	148112.59	99	0	3.87	90.22
Belgium	2,850.74	400504.36	0	60	0.18	14.69
Pakistan	129.91	6681.96	95	0	23.21	37.37
Japan	462.07	235855.4	98	51	0.53	16.56
Bangladesh	171.98	11900.04	99	0	25.88	22.96
Greece	3,348.97	534280.4	31	55	0.25	18.43
Tunisia	2,370.00	92874.74	92	0	1.15	15.33
Thailand	468.56	65857.8	99	0	9.62	29.71
Iraq	570.23	55400.49	99	0	2.26	15.14
Egypt	223.45	4645.86	99	0	0.54	25.25
Netherlands	1,313.99	488503.37	0	80	0.07	9.84
Portugal	2,503.59	540758.96	99	52	0.83	18.35
Bolivia	1,824.18	94977.68	99	30	10.73	69.51
South Korea	621.8	561928.9	98	85.1	1.93	25.21
Slovakia	3,689.76	470862.62	90	12	0.3	20.2
Myanmar	359.73	11696	91	0	38.12	40.28
Paraguay	2,903.52	116833.03	99	85	4.51	27.39
Sweden	2,069.04	253557.07	26.4	55	0.09	8.29
Guatemala	1,120.89	67481.38	55	0	2.31	70.32
Austria	2,398.65	638180.92	99	20	0.21	5.8
Georgia	4,512.62	483075.33	99	0	3.9	13.89
Sri Lanka	770.29	30775.3	96	0	3.45	13.67
Morocco	434.99	33947.24	99	0	8.35	22.11
Serbia	2,549.50	355997.42	99	10	0.63	10.5
Croatia	4,365.86	313594.99	98	30	0.65	8.4
Bosnia and Herzegovina	5,018.35	124010.6	95	0	1.6	7.26
Jordan	1,251.30	154795	86	0	0.13	15.14
Switzerland	1,621.54	503349.99	0	45	0.1	6.97
Kazakhstan	982.42	76724.72	99	0	1.56	18.79
Nepal	393.45	32768.55	96	0	72.19	29.37
Moldova	3,645.90	182264.37	99	0	3.79	21.42
Honduras	1,061.17	44658.42	99	70	6.16	17.65
Israel	1,273.89	504146.05	90	59.8	0.14	9.67
Lebanon	1,957.47	222690.71	0	0	1.02	14.8

Table 5: List of countries with COVID-19 deaths/million and COVID-19 incidences/million, BCG, Flu Vac coverage, TB deaths/100,000 and Flu deaths/100,000 on 31st December 2022.

Initially, we wished to determine how COVID-19 variants and COVID-19 vaccination coverage could have affected COVID-19 infection induced deaths from the start of the pandemic until December 2022. As seen in Table 1, at the initial phase of the pandemic (early-late 2020) it was difficult to determine the dominant strain causing the global pandemic. However, by the end of 2021 to the entire 2022 the dominant strain determining COVID-19 infection and deaths was the Omicron strain (21L, 22E and 22F). Additionally, countries which received at least 2 doses of the COVID-19 vaccination by 14th April 2022 displayed significantly reduced COVID-19 mortality compared to 24th May 2021 when the vaccination coverage was not prevalent across the different countries. This confirms the protective effect of the vaccination with respect to COVID-19 deaths (Figure 2).

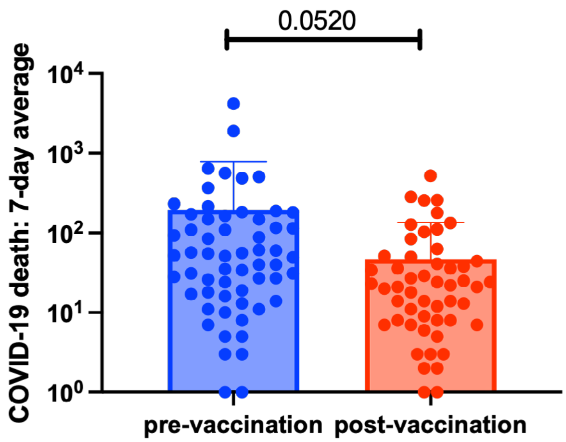

Figure 2: Covid vaccination causes a significant reduction in COVID-19 deaths across different countries: 62 countries were compared with respect to COVID-19 death:7-day average in pre-vaccination (24th May 2021) and post-vaccination (14th April 2022) conditions. A country is considered vaccinated against COVID-19 if the population has received at least two doses of the vaccine. Student t-test was performed to calculate statistical significance, $p<0.1$.

To understand the importance of pathogen exposure in providing cross protection against COVID-19 infection we started our analysis by calculating the extent of deaths due to Flu and TB and normalizing the values per 100,000 people. Subsequently, Spearman's correlation analysis was performed with both COVID-19 incidences/million and deaths/million, in which both the number of COVID-19 infection and deaths were normalized to the population of the country. We calculated the nature and significance of each correlation by using the "R_s" (Spearman's correlation coefficient) and p value respectively. TB deaths/100,000 showed a significant negative correlation with both COVID-19 deaths (Figure 3) and incidences (Figure 4) at all four time points suggesting the strong evidence of TB infection providing cross protection against COVID-19. Interestingly, TB deaths/100,000 showed a stronger negative correlation with COVID-19 incidences/million (R_s value range: -0.65 to -0.72 and p value<0.0001) than COVID-19 deaths/million (R_s value range: -0.27 to -0.44 and p value range: 0.03 to 0.0003).

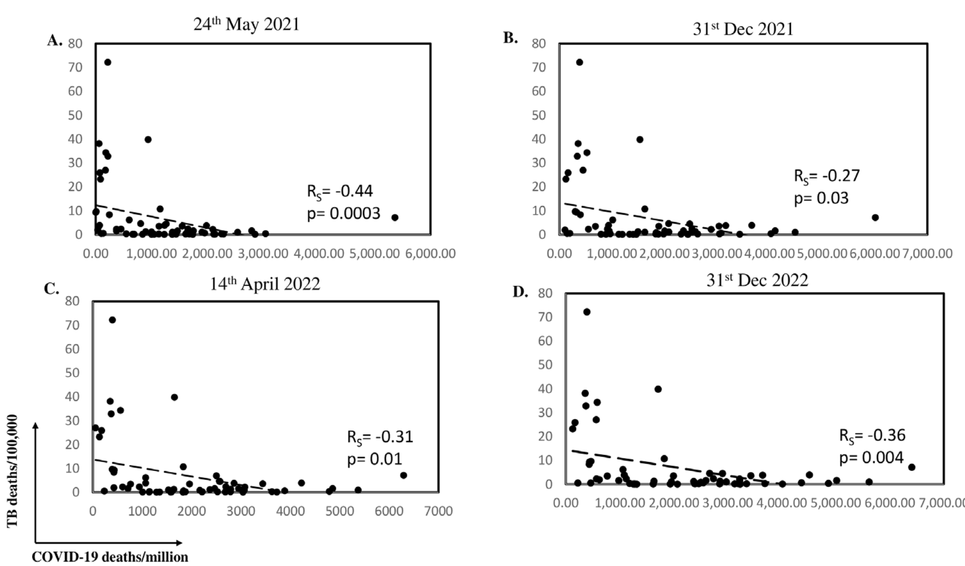

Figure 3: TB deaths/100,000 shows a significant negative correlation with COVID-19 deaths/million: TB deaths/100,000 was correlated with respect to COVID-19 deaths/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed and the correlation coefficient value (R_S) was calculated and the respective p values were also estimated for each graph. Correlation is considered statistically significant if $p<0.1$.

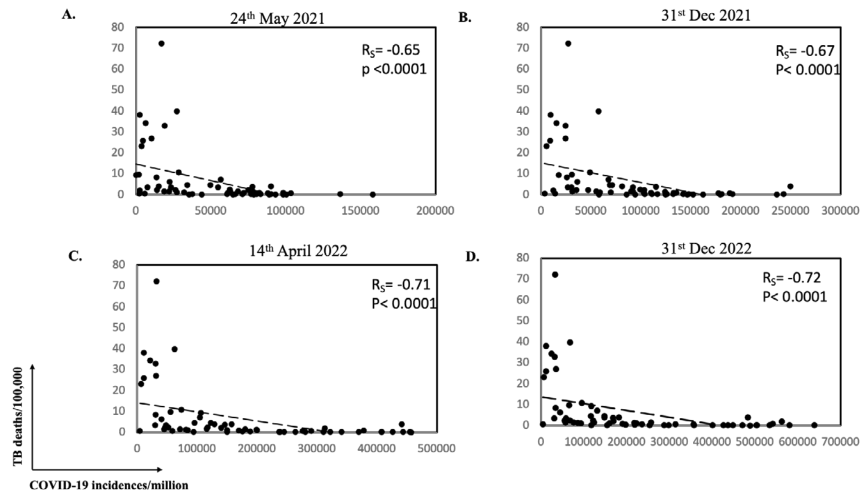

Figure 4: TB deaths/100,000 shows a significant negative correlation with COVID-19 incidences/million: TB deaths/100,000 was correlated with respect to COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed and the correlation coefficient value (R_S) was calculated and the respective p values were also estimated for each graph. Correlation is considered statistically significant if p<0.1.

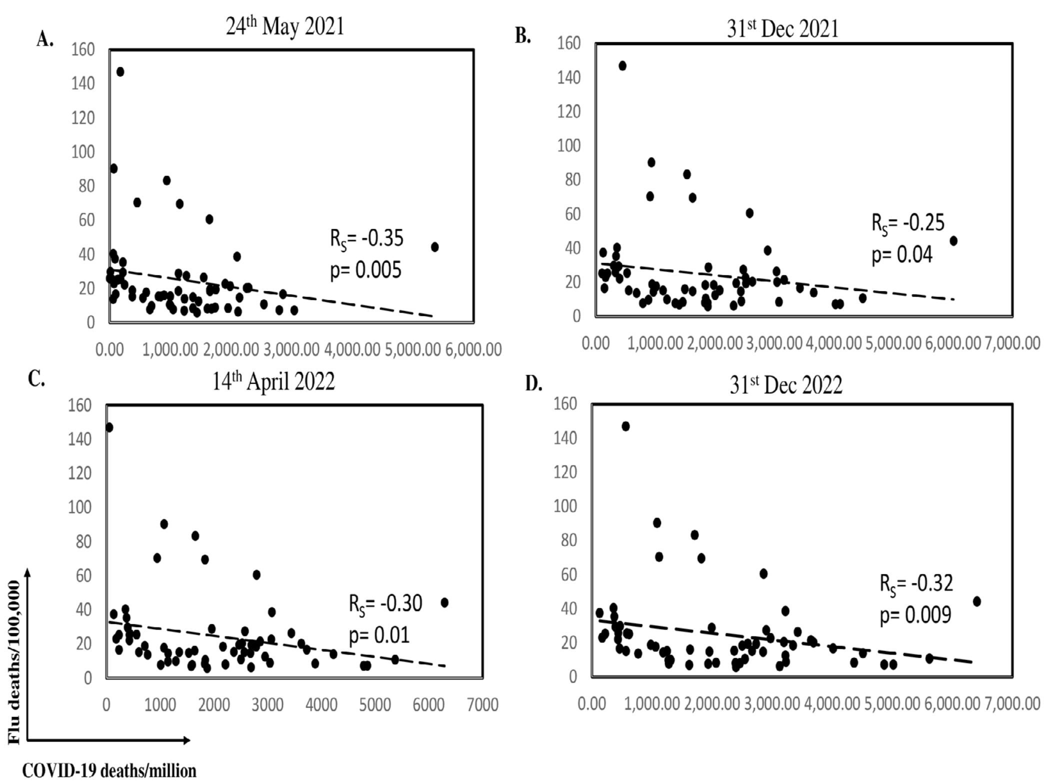

Figure 5: Flu deaths/100,000 negatively correlates with COVID-19 deaths/million: Correlation was performed with Flu deaths/100,000 and COVID-19 deaths/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed. Subsequently, the correlation coefficient value (R_S) was calculated and the respective p values were also estimated for each graph. Correlation is considered statistically significant if p<0.1.

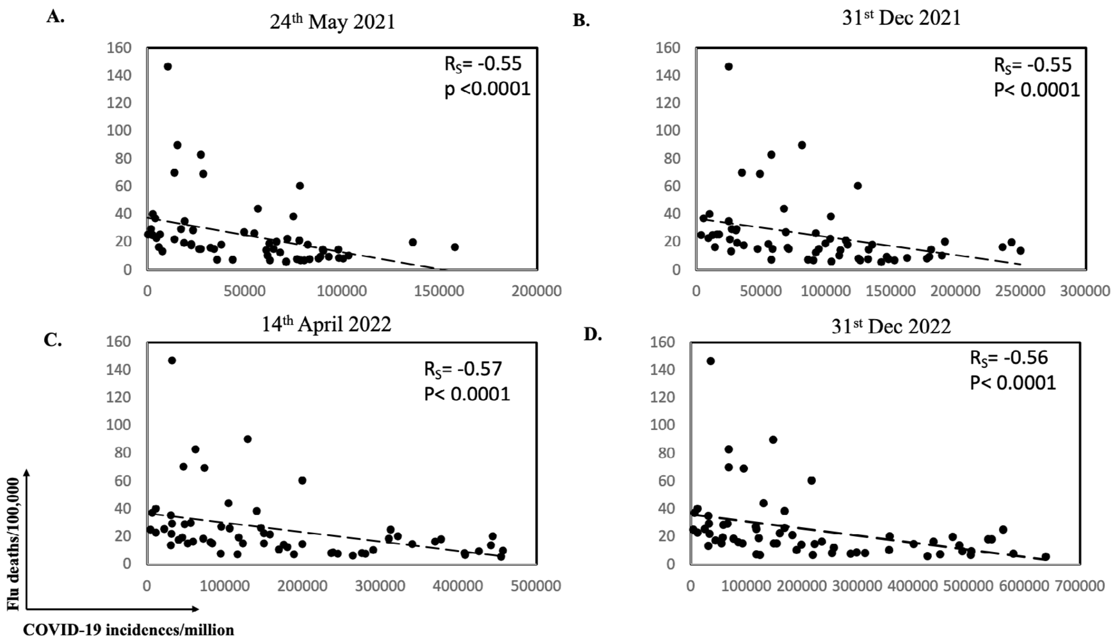

Figure 6. Flu deaths/100,000 negatively correlates with COVID-19 incidences/million at all three timepoints: Correlation was performed with Flu deaths/100,000 and COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed. Subsequently, the correlation coefficient value (R_S) was calculated and the respective p values were also estimated for each graph. Correlation is considered statistically significant if $p<0.1$.

Also, correlation analysis with Flu deaths/100,000 showed a similar trend where there was a significant negative correlation both with COVID-19 deaths (Figure 5) and incidences (Figure 6) which strengthened the importance of cross protection by two types of respiratory pathogens in determining the variation of COVID-19 infection and deaths in different countries. As there was a significant negative correlation with TB and Flu infection induced deaths it was important to perform correlation studies with BCG and Flu vaccination. BCG vaccination showed a significant negative correlation with COVID-19 deaths/million at three time points except 31st December 2021 (R_s = -0.20 and p = 0.11) (Figure 7). It is possible that this is due to variation in COVID-19 deaths across different countries over different timepoints. Considering there was still significant correlation in the remaining time points, the data suggested that BCG was still a major contributing factor in determining extent of COVID-19 infection in different countries. Additionally, there was significant negative correlation of BCG with COVID-19 incidences/million across all four time points further solidified the importance of BCG coverage playing a definitive role (Figure 9). Subsequently, Flu vaccination coverage positively correlated with both COVID-19 deaths (Figure 8) and incidences/million (Figure 10) across all the four timepoints. Therefore, countries with higher Flu vaccination coverage would naturally have less exposure to the infection thus making the population sensitive towards COVID-19 infection.

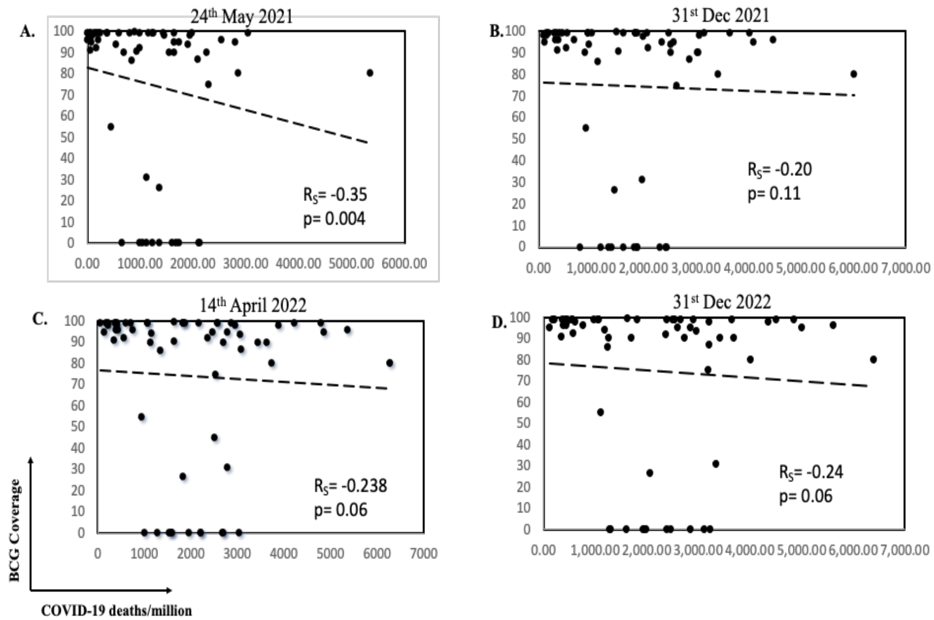

Figure 7: BCG coverage shows a negative correlation with COVID-19 deaths/million: Correlation graphs were plotted with respect to BCG coverage and COVID-19 deaths/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed and the correlation coefficient value (R_S) was calculated along with the respective p values. Correlation is considered statistically significant if $p<0.1$.

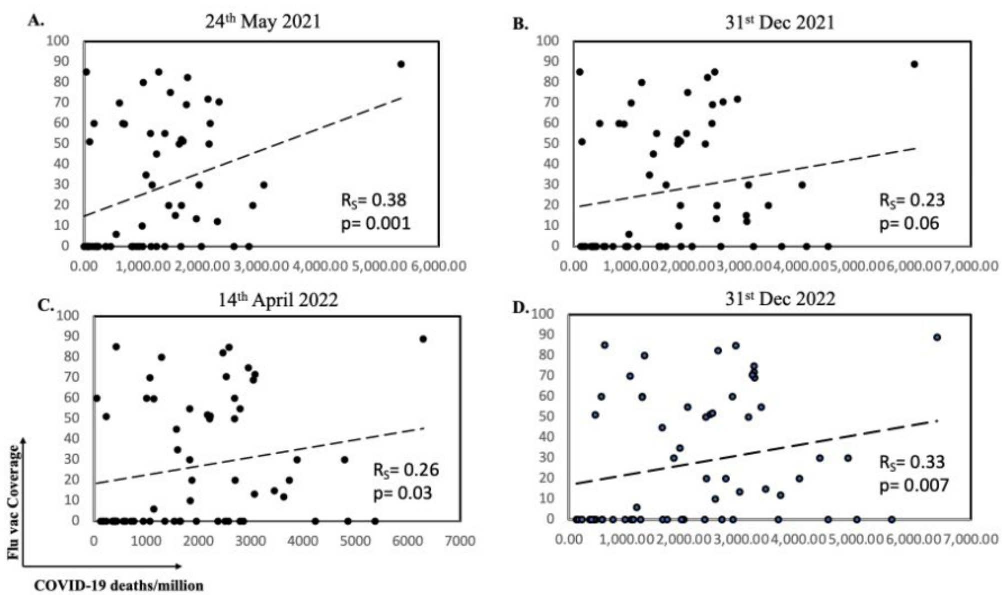

Figure 8: Flu vaccination coverage shows a positive correlation with COVID-19 deaths/million: Correlation graphs were plotted with respect to Flu vac coverage and COVID-19 deaths/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed to calculate the correlation coefficient value (R_S) along with the respective p values. Correlation is considered statistically significant if $p<0.1$. (Note Fig 8 has been replotted and changed, 31 Dec 2022 data - no change in interpretation of data)

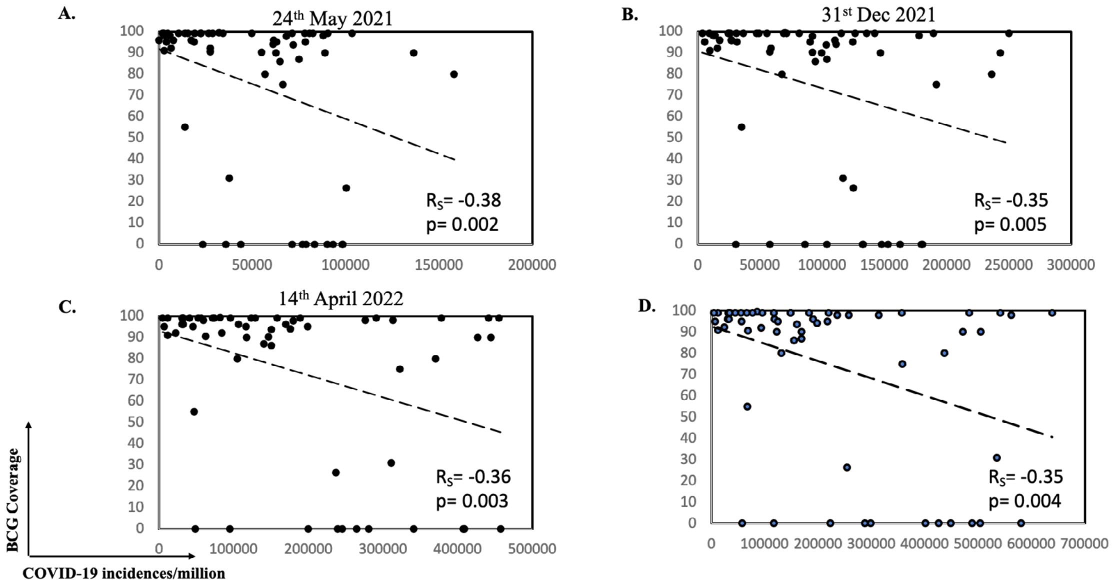

Figure 9: BCG coverage shows a significant negative correlation with COVID-19 incidences/million: Correlation graphs were plotted with respect to BCG coverage and COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and 31st December 2022. Spearman's correlation was performed and the correlation coefficient value (R_S) was calculated along with the respective p values. Correlation is considered statistically significant if $p<0.1$.

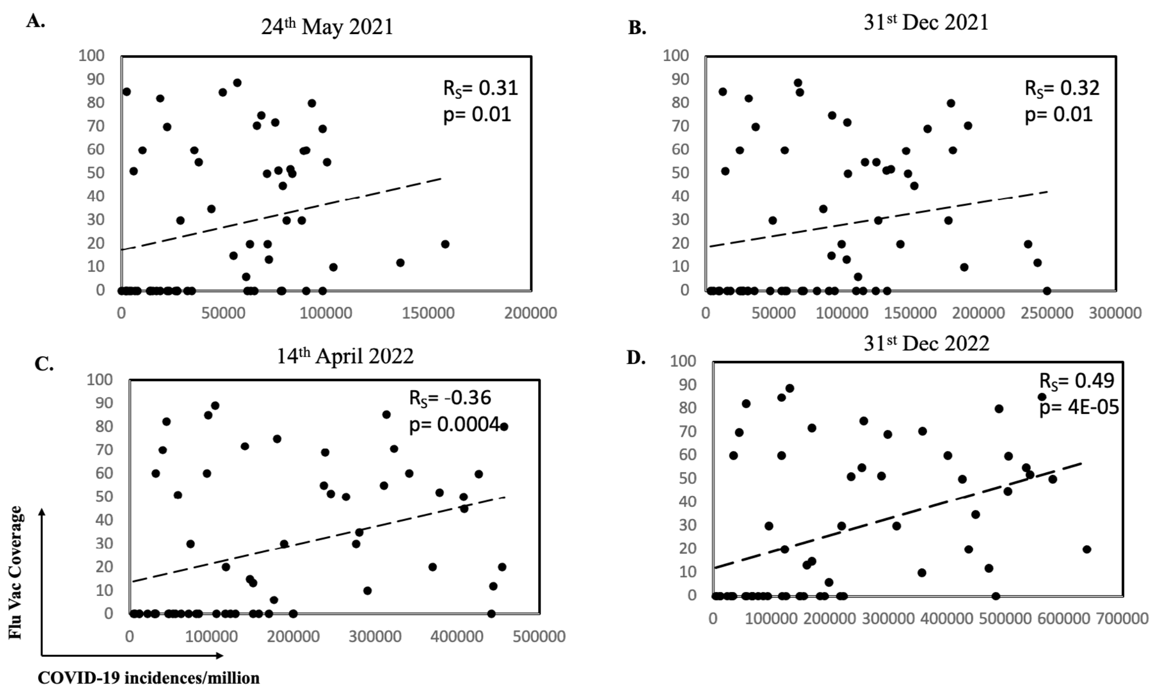

Figure 10: Flu vaccination coverage shows a strong positive correlation with COVID-19 incidences/million: Correlation graphs were plotted with respect to Flu vac coverage and COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Spearman's correlation was performed to calculate the correlation coefficient value (R_S) along with the respective p values. Correlation is considered statistically significant if $p<0.1$.

As pathogen exposure was effectively correlating with COVID-19 infections and deaths, we wished to understand whether the heterogeneity in countries with TB and Flu infections affected COVID-19 infections and deaths. To test this, we segregated the 62 countries based on extent of deaths due to TB and Flu. Deaths were considered high ("hi") if deaths were >= 25 deaths/100,000 and low ("lo") when deaths were <=25 deaths/100,000. Using these demarcations, we were able to segregate the countries into three basic groups: $TB^{hi}Flu^{hi}$, $TB^{lo}Flu^{hi}$ and $TB^{lo}Flu^{lo}$ [16]. It was observed that countries with both high TB and Flu deaths were the most protected against COVID-19 incidences (Figure 12) and deaths/million (Figure 13). On the contrary, countries with both low TB and Flu deaths were the most sensitive against COVID-19 infection. Interestingly, countries with low TB deaths but high Flu deaths displayed less COVID-19 incidences compared to countries with low TB and Flu deaths (Figure 12).

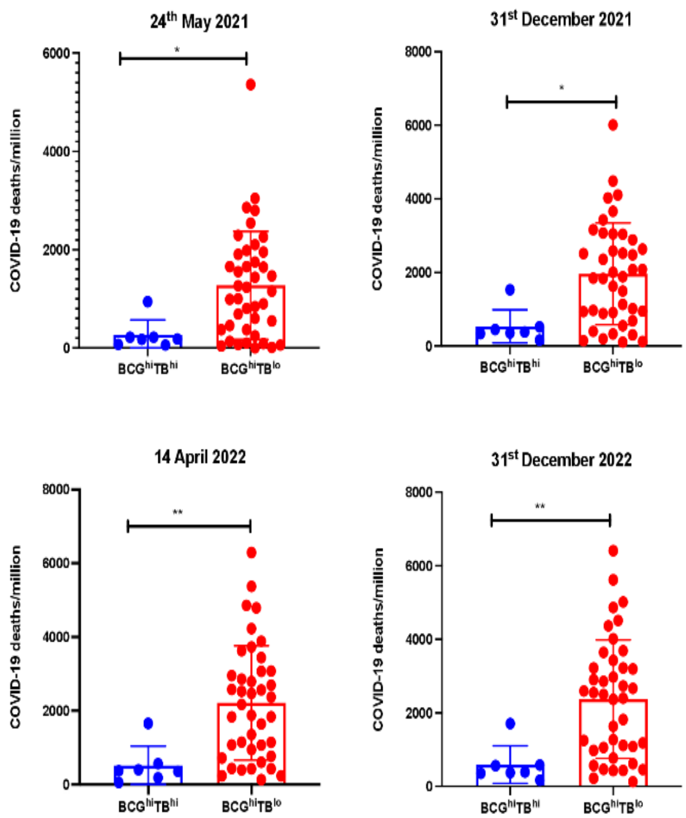

Figure 11: Countries with high BCG coverage and TB deaths have better protection from COVID-19 deaths: Countries with high BCG coverage were divided using TB deaths as the differentiating criteria. $BCG^{hi}TB^{hi}$ and $BCG^{hi}TB^{lo}$ groups were then compared for COVID-19 deaths/million for four mentioned timepoints: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Student's t-test was used to calculate statistical significance. Data is considered statistically significant if $p<0.1$.

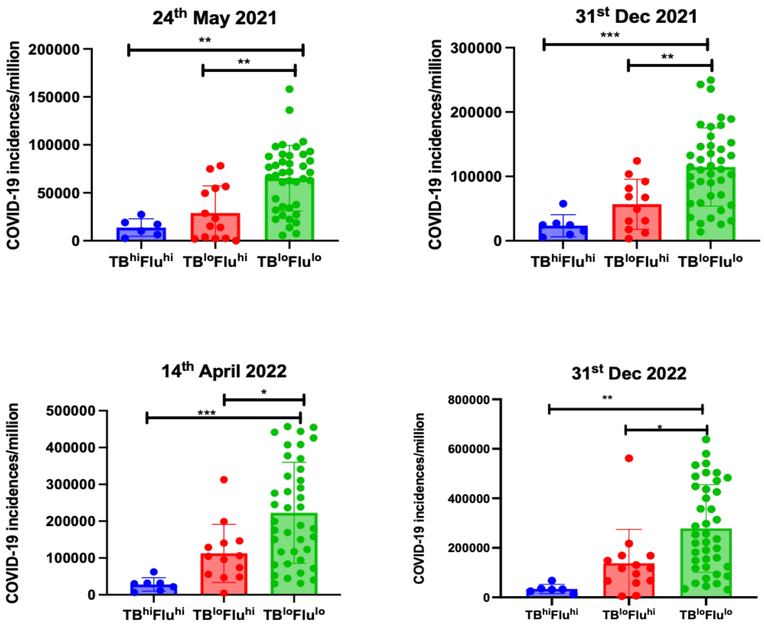

Figure 12: Countries with high TB and Flu deaths have the lowest COVID-19 incidences/million: Countries were grouped based on deaths due to TB and flu infection. The countries were then compared with respect to COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. One-way ANOVA was performed to calculate statistical significance, p<0.1.

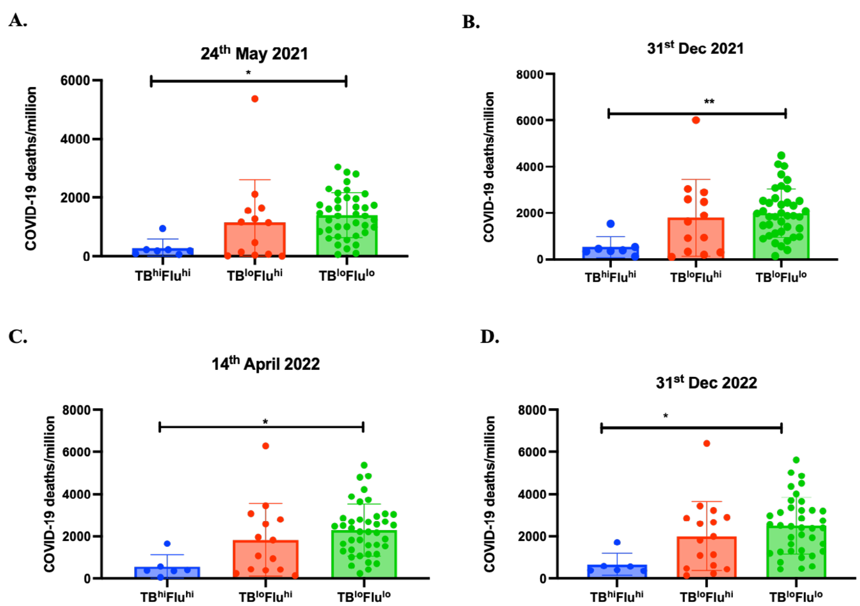

Figure 13: Countries with high TB and Flu deaths are most protected from deaths due to COVID-19: Countries were grouped based on deaths due to TB and flu infection. The countries were then compared with respect to COVID-19 deaths/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. One-way ANOVA was performed to calculate statistical significance, p<0.1.

Considering both TB deaths and BCG coverage had a strong negative correlation with both COVID-19 incidences/million and deaths/million, we asked the subsequent question: whether the extent of COVID-19 infection was dependent on a preferred factor out of the two. We thus selected countries which had high BCG coverage and divided the countries based on high and low TB deaths. We thus had two groups: $BCG^{hi}TB^{hi}$ and $BCG^{hi}TB^{lo}$. Figure 11 and Figure 14 shows that countries which had high BCG coverage and high TB deaths had significantly less COVID-19 cases and deaths than countries which only had high BCG coverage. Hence, high BCG coverage and TB exposure in the former have an additive effect in promoting the best protection against COVID-19 infection and deaths compared to latter which gets protection only due to high BCG coverage.

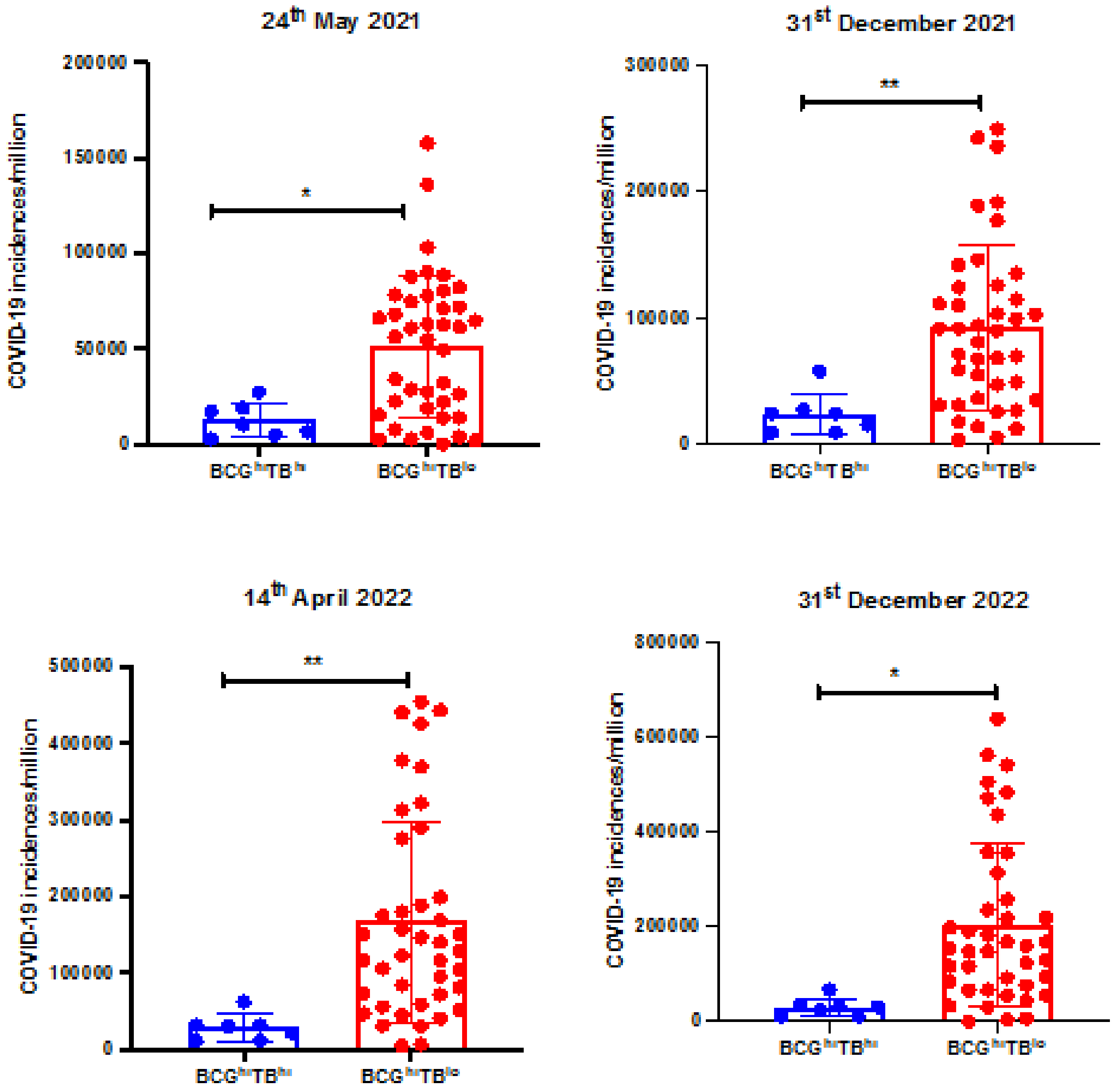

Figure 14: Countries with high BCG coverage and TB deaths have better COVID-19 protection: Countries with high BCG coverage were divided into two main groups using TB deaths as the differentiating criteria. $BCG^{hi}TB^{hi}$ and $BCG^{hi}TB^{lo}$ groups were compared for COVID-19 incidences/million for four timepoints: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. Student's t-test was used to calculate statistical significance. Data is considered statistically significant if $p<0.1$.

Finally, we addressed the roles of BCG and Flu vaccination as contrasting correlation patterns were observed. The segregation pattern was as follows: countries were segregated based on the presence or absence of a particular vaccination which was denoted as “+” or “-“ respectively. For countries with both vaccination programs, the segregation pattern was based on the extent of vaccination coverage. Countries with <50% coverage of a particular vaccination was considered as low coverage (“lo”). On the other hand, >50% coverage was considered high coverage (“hi”). Using these parameters countries were segregated in four distinct groups: $BCG^+FluVac^-$, $BCG^-FluVac^+$, $BCG^{hi}FluVac^{hi}$ and $BCG^{hi}FluVac^{lo}$ [16]. These four groups were first compared using COVID-19 incidences/million where it was evident that countries with only BCG vaccination had the lowest COVID-19 incidences/million whereas countries with only Flu vaccination had the highest (Figure 15). However, this observation was not seen when analysing COVID-19 deaths/million (Figure 16). This could possibly be because countries belonging to the group $BCG^+FluVac^-$ had more variation in the extent of deaths at these later time points since countries such as India, South Africa etc. have now higher deaths due to COVID-19 over time which has caused the overall significant differences to disappear.

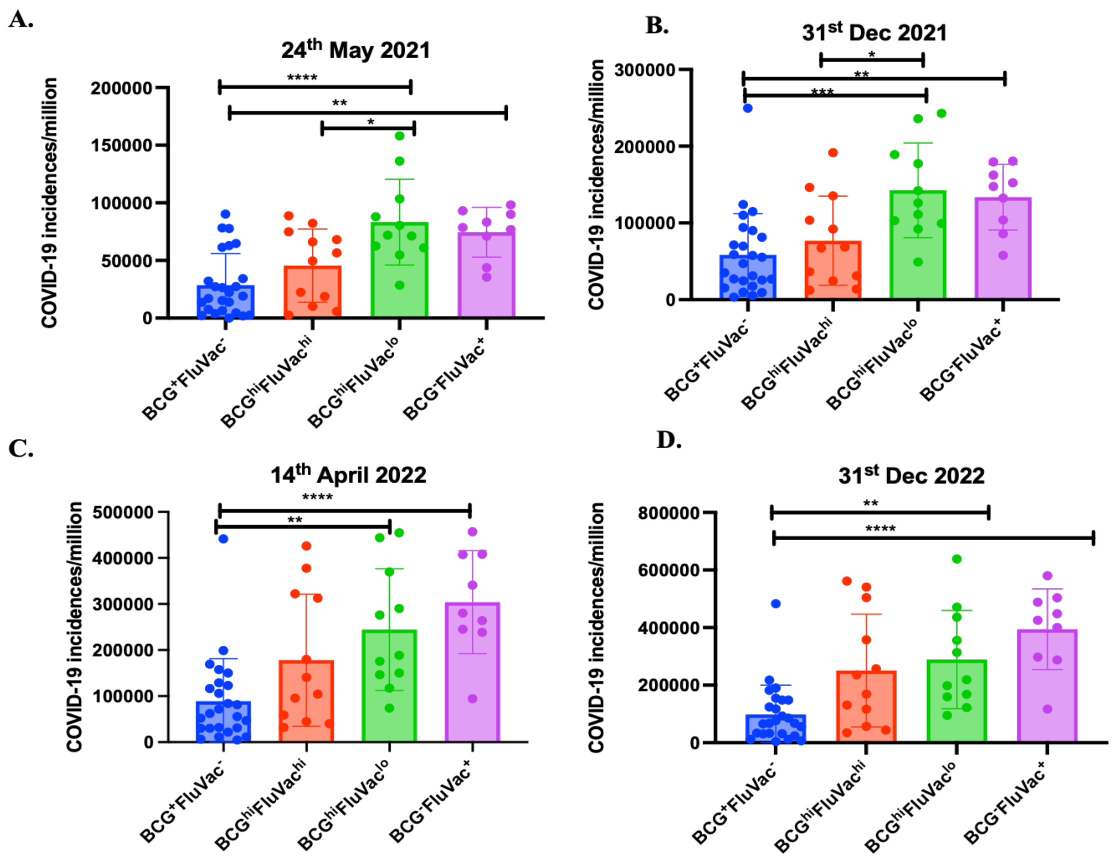

Figure 15: $BCG^+FluVac^-$ countries are the most protected from COVID-19 infection: Countries were segregated based on extent of BCG and Flu vaccination coverage and then compared with respect to COVID-19 incidences/million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. One-way ANOVA was performed to calculate statistical significance, p<0.1.

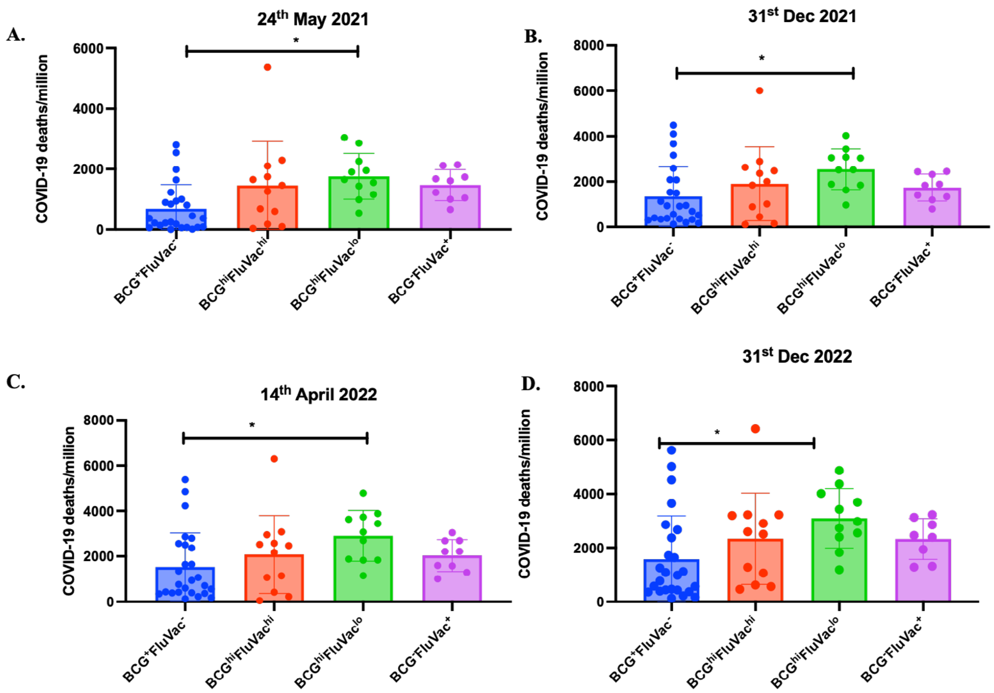

Figure 16: $BCG^{+}FluVac^{-}$ countries are more protected with respect to deaths due to COVID -19 than countries which are $BCG^{hi}FluVac^{lo}$: Countries were segregated based on extent of BCG and Flu vaccination coverage and then compared with respect to COVID-19 deaths/ million at four different time points: **A.** 24th May 2021, **B.** 31st December 2021, **C.** 14th April 2022 and **D.** 31st December 2022. One-way ANOVA was performed to calculate statistical significance, $p<0.1$.

Discussion

Pre-existing infections may modulate responses to newer infections by pathogens [7,9,10]. In this study, we followed the COVID-19 pandemic and showed that countries with high flu and tuberculosis deaths showed less COVID-19 incidences as well as deaths (Figures 1, 3-6). Also, there are opposing roles of vaccine. Countries with high flu vaccinations show greater COVID-19 incidences and deaths (Figures 8 and 10). On the other hand, countries with high BCG vaccination show lower COVID-19 incidences and deaths (Figures 7 and 9). In our previous study based on 2020 data, correlations were seen only with respect to COVID- 19 deaths [16]. However, in the current study as the pandemic has progressed correlations are seen with both COVID-19 incidences as well as deaths.

There are several points that are notable in this study. First, this study involves a large number of countries and is global in nature. Second, the number of cases as well as deaths have been extracted from various official sites. Third, fluctuations in cases and deaths may vary in different countries across various time points; however, this does not appear to affect the overall trends. For example, the number of cases and deaths during the second wave in India in 2021 were very high. Despite this observation, India seems to have weathered the effects of the COVID-19 pandemic well. From the point of immune responses, it is possible that countries with high exposure of pathogens lead to higher non-specific immunity. Indeed, flu vaccinations have been shown to protect against COVID-19 infections [21,22], perhaps due to an increase in non-specific immunity. However, our epidemiological study shows the opposite effect of flu infections, perhaps due to long-term effects. Similar to our observation, another study has shown a negative correlation between COVID-19 deaths/100,000 and flu-pneumonia deaths per year per 100,000 in various countries [23]. In fact, flu infections are known to increase non-specific immunity [24,25]. Also, infections by some viruses may interfere with the replication of other viruses, a phenomenon known as viral interference. Flu infections are known to affect the replication of other viruses [26,27]. In fact, coinfections studies have shown that flu virus infection lowers the replication of the SARS-Cov2 virus due to an early burst of Type I Interferon [28]. Interestingly, the chances of testing positive for SARS-Cov2 is lower in patients suffering from influenza although those infected with both viruses had a higher risk of mortality compared to those infected with either virus [29]. Clearly, these studies highlight the importance of virus-virus interactions that may modulate immune responses in the respiratory track.

Tuberculosis infections have been shown to lower the ACE2 receptor [30]. Thus, it is possible that countries exposed to the tubercle bacilli may lower the amounts of symptomatic SARS-COV2 infections. Also, mycobacterial components are known to boost immune responses [31]. BCG vaccination is observed in countries with high numbers of tuberculosis cases. In fact, the clinical efficacy of BCG as a pediatric vaccine is well established and it is often one of the first vaccine to be administered to kids. BCG is one of the oldest and safest vaccine that is well known to increase non-specific immunity to several pathogens and lower mortality [32,33]. BCG is one of the earliest vaccines given to kids and it is likely that the long-term effects of BCG are due to the induction of trained immunity which leads to epigenetic reprogramming of immune responses [34]. One needs to be aware that there are different strains of BCG which may also affect vaccination efficacies [35]. It is important to note that this vaccine has been proposed to initially non-specifically protect vulnerable groups, for example kids and elderly, from newer infectious agents as they arise [16].

It is remarkable that despite the differences in socio-economic status, geographical locations, differences in cultural traditions, gross domestic product, population size and densities etc there appears to be a correlation between BCG vaccinations and lower COVID-19 deaths (Figure 7). This aspect has been observed in several [36-38] but all studies [39]. Although the effects of BCG are not accepted by all, at least two reports have shown that the effects of BCG are seen during best the early stage of the disease, but the effect wanes with time as the pandemic progresses [37,40]. Our previous study has shown that some countries in South America, e.g. Brazil and Mexico, with high BCG coverage did show a lag but higher mortality was observed later as the pandemic progressed. Perhaps, it is not a good idea to study all countries that have high BCG coverage as a whole. Due to the heterogeneity in responses, our ability to segregate BCG high vaccination coverage with those that show low or high tuberculosis deaths led us to identify the countries with high BCG vaccination coverage and high tuberculosis deaths to be the most protected against COVID-19. In fact, our study demonstrated that countries that showed the lowest mortality were ones with high BCG vaccination coverage together with high deaths due to tuberculosis (Figure 11). Perhaps, the combination of BCG vaccination together with periodic exposure to the tuberculosis bacilli is important to keep the immune system in a heightened state for better protection against COVID-19 [16].

It is, therefore, important to study the clinical efficacy of BCG vaccination. Here too, BCG has shown efficacy is some [41,42] but not all studies [43]. The reasons for these are probably due to the heterogeneity in the groups: differences in countries, e.g. health care workers in South Africa [43] versus patients with Type I diabetes (a vulnerable group) in Boston, USA [41], duration of trial, differences in BCG strains used, possible previous exposure to pathogens etc. Notably, in the latter study, the BCG vaccinated group suffered lesser incidences of infectious diseases compared to the control unvaccinated group [41]. In another independent study on health care workers, the BCG vaccinated group demonstrated lower amounts of cytokines such as TNF-alpha and IL6 in response to SARS-CoV2 which is consistent with the immunomodulatory effects of BCG [42]. Finally, intravenous inoculation with BCG led to lower viral loads and protection compared to the control group mice expressing the human ACE2 receptor upon challenge with SARS-CoV2 [44]. Also, a study has shown that health workers inoculated with a killed non-pathogenic mycobacterial strain and an immunomodulator [45], *Mycobacterium indicus pranii*, showed lower incidences and severity of COVID-19 [46]. Another clinical study has shown that patients with severe COVID-19 inoculated with killed *Mycobacterium indicus pranii* showed better clinical symptoms of recovery compared to the control group [47].

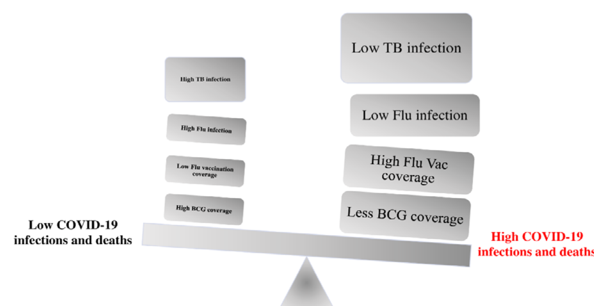

Figure 17: Graphical abstract mentioning the factors that play a determining role with regards to COVID-19 infections and deaths in different countries: The rate of infection and death due to COVID-19 in a country is determined by various factors such as TB and Flu infection and vaccination coverage such as Flu vaccination coverage (Flu Vac) and BCG which provides specific and cross protective immunity against the pathogen.

It is difficult to pinpoint one major factor that plays the lead cause in determining both the extent of COVID-19 incidences and deaths. Clearly, there are multiple factors that are responsible for COVID-19 deaths across various countries. Despite this, it is remarkable that our study which was initiated in 2020 and now in 2021 and 2022 has been able to show that countries with higher flu and tuberculosis deaths are more protected against COVID-19 (Figure 17).

Conclusions

It is likely it could be a combination of both high pathogen exposure and high BCG coverage which eventually "tips" the balance towards lower Covid-19 induced infection and mortality shown in **Figure 17.** We believe that our study contributes to the understanding of the roles of multiple factors that are possibly involved in regulating COVID-19 infection.

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