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REVIEW

BCG as a game-changer to prevent the infection and severity of COVID-19 pandemic?

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Abstract The impact of COVID-19 is changing with country wise and depend on universal immunization policies. COVID-19 badly affects countries that did not have universal immunization policies or having them only for the selective population of countries (highly prominent population) like Italy, USA, UK, Netherland, etc. Universal immunization of BCG can provide great protection against the COVID-19 infection because the BCG vaccine gives broad protection against respiratory infections. BCG vaccine induces expressions of the gene that are involved in the antiviral innate immune response against viral infections with long-term maintenance of BCG vaccine-induced cellular immunity. COVID-19 cases are reported very much less in the countries with universal BCG vaccination policies such as India, Afghanistan, Nepal, Bhutan, Bangladesh, Israel, Japan, etc. as compared to without BCG implemented countries such as the USA, Italy, Spain, Canada, UK, etc. BCG vaccine provides protection for 50–60 years of immunization, so the elderly population needs to be revaccinated with BCG. Several countries started clinical trials of the BCG vaccine for health care workers and elderly people. BCG can be uses as a prophylactic treatment until the availability of the COVID-19 vaccine.

Introduction

The recent COVID-19 outbreak from Wuhan city in China and spread globally with 4,648,479 confirmed cases and 309,008 deaths (as of May 16, 2020).[1] SARS-CoV2 is pathogenically stronger than the previous outbreaks of coronavirus (Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS)).[2] SARS-CoV2 is transmitted from one person to another during sneezing or coughing droplets, reported in family settings as well as hospitals[3] and is also transmitted from contaminated surfaces or contaminated consumables by self-inoculation through the eyes, mouth

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and nose.[4,5] SARS-Cov-2 is closely related to the previous SARS coronavirus and the origin of SARS-Cov-2 is from the same reservoir bat host.[6] Zoonotic transmission of the SARS coronavirus between bat and human by intermediate hosts palm civets and raccoon dogs,[7] but the intermediate hosts for COVID-19 transmission within bats and humans are still unknown. All highly pathogenic SARS coronavirus (MERS-CoV, SARS-CoV, and SARS-CoV2) are related to the bat coronavirus genus compared to low pathogenic coronavirus (HCoVHKU1, HCoV-OC43, HCoV-NL63, and HCoV-229E). There is no curative therapy or vaccine for all types of coronaviruses to date, although a few vaccines have been developed and registered in clinical trials against the SARS-Cov-2 virus.[8] COVID-19 enters into the host cell by using their transmembrane spike (S) proteins. Spike proteins are glycoproteins that bind with host cells ACE-2 cell membrane receptors.[9] Current data is emphasizing that the available vaccines prevent viral infections by activation of the antiviral immune response, such as BCG. According to the literature available, BCG activates the human immune system against several types of viruses such as human Respiratory Syncytial Virus (hRSV), and human papillomavirus (HPV).[10] This review deals with the importance of BCG in the prevention of COVID-19 expansion and its severity. Literature and surveys exhibiting the COVID-19 spread and severity are much greater in those countries which did not have any BCG vaccination regimen.

Different countries implemented different policies for BCG immunization because of their undefined efficacy.[11] Various countries, such as India, Japan, etc., are having a universal BCG immunization program, whereas other countries such as Canada, USA, Italy, Spain, etc. implemented for the high-risk community. BCG immunization procedures differ from one country to another in favor of age, administration route, and doses of the vaccine. Most of the countries previously used three booster doses of BCG vaccine but nowadays only a single dose is used by an intradermal route at an early age, around the first year of life in newborns.[12] No scientific evidence is available for booster doses or revaccination of BCG[13] so the World Health Organization (WHO) Global Programme on Tuberculosis and Vaccines in 1995 did not recommend repeat BCG schemes. The WHO recommends that one dose of the BCG vaccine should be administered in all neonates of countries with a high incidence of TB.[14] Immunization policies are revised or changed country-wise from time to time, depending on health policies, variation in evidence, community perception, the difference in TB, and comorbid incidence (HIV).[11] The meta-analysis found the variation in BCG vaccine efficacy reduced the TB risk by 50% in controlled trials and the duration of the vaccine susceptibility remains unknown.[15,16] One study reported that the TB mortality attributed to vaccination in a 20-year BCG and placebo-controlled trial fell by 82%.[17,18] In that clinical trial, vaccination started from 1935 to 1938, and prospective TB cases finding by 1947.[18] Another controlled trial stated the efficacy of the BCG vaccine with long term protection, approximately 60 years of age after vaccination.[19]

Why BCG vaccine only

BCG vaccination provides a wide range of safety against bacterial and viral infections but there is no evidence regarding BCG, whether it directly reduced the COVID-19 infection or not.[10] A study has shown the correlation between BCG vaccination and COVID-19 infection, and studies have also shown fewer COVID-19 cases in universally implemented countries. The universal use of the BCG vaccine for the community might decrease the spread of COVID-19, and it can help to stop the transmission of the disease.[20] Randomized controlled trials are needed to determine the role of BCG vaccination in immune activation against COVID-19. Nevertheless, BCG has shown a number of side effects (blood in urine, joint pain, nausea, vomiting, painful urination, etc.) in immune-compromised people and pregnant women.[21] The BCG vaccine may boost the immune system's ability to fight off pathogens, including the deadly coronavirus. Various investigations showed that the BCG vaccine also defends against viral infections affecting the respiratory tract in humans and mice. BCG protects against bacterial infection and also protects against respiratory viral infections.[10,22] In this study, mice who have BCG vaccination before infection have low Influenza A load in their blood with less damage to the lungs.[23,24] Several studies have stated that the BCG vaccine stimulates the resistance against viral infection in animals by inducing the epigenetic modifications in macrophages, monocytes, dendritic cells, and other immune cells. These immune cells enhance the production of pro-inflammatory cytokines such as INF-γ, TNF-α, and IL-1b, and develop the resistance for herpes type 1 and 2 viruses.[24,25] These studies provide an idea that BCG vaccination might activate the immune system against viral infection. Thus, there is a path by which vaccine provides protection and reduces the risk of severely infectious diseases. Further studies also revealed that the BCG vaccine increases resistance in laboratory animals against other viruses, and ensure that it can be uses as a method of COVID-19 treatment. COVID-19 spread extensively in those countries which did not implement BCG vaccination, such as the USA, Italy, Spain, France, Germany, South Korea, Iran, etc. whereas those countries that have implemented BCG vaccination earlier showed a slower spread and low severity of COVID-19. Italy implemented the BCG vaccination. Four clinical trials are recruited in clinicaltrial.gov with BCG vaccination to prevent or reduce the severity of COVID-19 in the elderly population and Health Care Workers.[26] To manage the COVID-19 infection, the whole world is busy with developing the vaccine against this pandemic based on proteins, RNA, DNA, and viral vectors technology. Few of them are registered in clinicaltrials.gov, such as the Minigene vaccine, Adenovirus type 5 vector recombinant vaccine, Pathogen-specific aAPC vaccine, ChAdOx1 nCoV-19/MenACWY/COV001, bacTRL spike vaccine, and mRNA-1273 and immunize the population against the COVID-19 infection (clinicaltrials.gov).

The **minigene** and **Pathogen aPAC** vaccines are synthetic vaccines developed by using the conserved domains of COVID-19's polyprotein protease, and structural proteins. The COVID-19 virus interacts with ACE-2 receptors of host cells by using the Spike protein. Viral replication inside the host cell depends on the molecular mechanisms of viral proteins. This clinical trial aims to develop and examine the COVID-19 minigenes vaccine, based on multiple viral genes. For the expression of viral genes and immunomodulatory genes a powerful lentivirus (NHP/TYF) is used as a vector,

which might activate T cells and modify the dendritic cells and antigen presenting cell (aAPC).[27,28]

Adenovirus type 5 vector recombinant vaccine trial is planned to estimate the potential to activate the immune system and safety of Ad5-nCoV, full-length spike (S) protein encodes for SARS-CoV-2.[29]

bacTRL spike vaccine contains live *Bifidobacterium longum* as colony-forming-units (CFU), which is designed to deliver synthetic DNA with spike Proteins of SARS-CoV-2 containing plasmids.[30]

mRNA-1273 vaccine trial is planned to evaluate the immunogenicity, reactogenicity, and safety of the mRNA vaccine constructed by ModernaTX, Inc. It is encapsulated by a novel lipid nanoparticle (LNP) that encodes SARS-CoV-2's prefusion stabilized spike (S) protein.[31] mRNA vaccines are essential for generating the specific immune response against infections by immune system activation with quickly exposing the immune cells to the antigen. mRNA vaccine development is very critical and problematic because the efficacy of the mRNA vaccine could be altered at the time of manufacturing and can cause side effects.

Proteins encoded by synthetic mRNA of interest are used as a cellular mRNA to the immediate translation of the antigen genes.[32] The efficacy of mRNA vaccines can be improved by choosing or developing appropriate methods. Developers faced several technical problems at the time of mRNA vaccine production and might overcome this by verifying whether the vaccine works accurately or not.[33] Unintentional properties of the mRNA vaccine can produce an unwanted immune response. To overcome this problem, requires designing the mRNA vaccine sequences and confirming that they should mimic those mRNAs transcribed by mammalian cells. Successful delivery of the vaccine into the cell is a major challenge because free RNA quickly degrades in the body. For successful delivery of the RNA, the vaccine RNA strands should be incorporated with a bigger molecule that provides stability into nanoparticles or liposomes. Several mRNA vaccines have to be frozen or refrigerated like conventional vaccines.[33]

Role of BCG in activation of immune system against the viruses

After BCG vaccination, BCG initiates the body's immune response against the foreigner BCG antigen. At the site of vaccine administration, local immune cells (Dendritic cells, neutrophils, and macrophages) get activated and interact with the bacterial colony.[34,35] Immune cells recognize the pathogen through the different types of pathogen-associated molecular patterns (PAMPs) and pathogen recognition receptors (PRRs), which preserved molecular signatures of bacteria and viruses. PAMPs like peptidoglycans, cell wall proteins, lipopolysaccharides, mycolic acids, glycoproteins, etc. bind with PRRs that present on immune cells. Toll-like receptors such as TLR2 and TLR4 are associated with BCG recognition.[34] TLRs perform an essential function in pathogen recognition for a different variety of PAMPs. It is known that six represent a subclass of TLRs that recognize the ligands of viruses.[36] TLR2 and TLR4 receptors are present on the cell surface activated by viral glycoproteins or by other foreigner proteins produced by extracellular milieu. Antiviral innate immune activation depends on the particular type of TLR signaling mechanism that is stimulated through the particular type of pathogen.[36–40] Studies have shown that BCG expressed different proteins that activate TLRs and activate macrophages and dendritic cells. After the activation of these cells, they produce pro-inflammatory cytokines.[41] DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a C-type lectin that interacts with bacterial wall constituents, and helps to recognize and internalize the process of BCG.[42] Dendritic cells get activated after interactions with the pathogen and initiate dendritic cell migration and maturation, which is described by the upregulation of CD40, CD80, CD83, and CD86 co-stimulatory molecules.[43] Antigen 85 expresses on the M.TB surface also present on the BCG surface, which induced the secretion of tumor necrosis factor (TNF-α), interleukin-6 (IL-6), and, interleukin- 1beta (IL-1β).[44,45] It could activate immune cells by generating pro-inflammatory cytokines.[43] Adaptive immune response initiates by antigen presentation when an antigen-presenting cell presents an antigen peptide with major histocompatible complex (MHC) molecules to naive T cells, found spleen to be the most affected organ or any secondary lymphoid tissues.[46] In vitroandin vivo studies have reported that the skin dendritic cells having BCG inside migrate to the lymph nodes and activate both types of T cells $CD4^+$ and $CD8^+$T cells by the secretion of TNF-α, IL-6, and IL-12.[47–50] Surprisingly, it has been stated that the stimulation of antigen-specific T cell responses by the BCG infected dendritic cells is induced by infected neutrophils.[51]

After BCG vaccination, adaptive immune cells ($CD4^+$ and $CD8^+$T cells) become activated, initiate the immune response against the BCG antigens[46,52] and increase the secretion of IFN-γ. IFN-γ improves the potential against mycobacteria of the macrophages,[45,46] and it also activates against viruses. IFN-γ, the specific cell type of cytokine that involved in B cells activation and differentiation, B-cells differentiated into plasma B cells, and memory B cells where plasma B cells produced antibodies against the particular antigen. Activated $CD8^+$ T cells proliferate into specific $CD8^+$ T cells against BCG antigen and persist for ten weeks in peripheral blood.[53] Specific $CD8^+$T cells against an antigen released IFN-γ, and also express the perforins and granzymes to the cytotoxic activity of $CD8^+$T cells.[53,54] $CD4^+$ and $CD8^+$ T cells specific for BCG antigen converted into effector memory T cells with their functional features of IFN-γ secretion.[55,56] One study has reported the strong lymphoproliferative activity of effector memory T cells, sustained for many months, against the TB antigens in mice.[56]

BCG can be a game changer for SARS-CoV-2 infection

Several clinical trials started to treat the SARS-CoV-2 using the BCG vaccination. A study has been published by the New York Institute of Technology (NYIT) exploring that the BCG vaccine could be a game-changer in the fight against SARS-CoV-2.[20] The BCG vaccine is used all over the world (except the USA, Germany, Spain, Italy, etc.) to defeat TB infection. The researchers observed that the countries without universal BCG vaccination policies, are having ten-times

Table 1 SARS CoV-2 infection in non-BCG implemented countries.

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Deaths as %	Total Recovered Cases	Recovered cases as %
1.	Andorra	761	49	6	604	79
2.	Anguilla	3		0	1	33
3.	Antigua and Barbuda	25	3	12	19	76
4.	Australia	7035	98	1	6353	90
5.	Bahamas	96	11	11	41	43
6.	Bahrain	6583	12	0	2640	40
7.	Barbados	85	7	8	65	76
8.	Bermuda	122	9	7	66	54
9.	Canada	74,613	5562	7	36,895	49
10.	Caribbean Netherlands	6		0	6	100
11.	Cayman Islands	94	1	1	55	59
12.	Channel Islands	549	48	9	457	83
13.	Curacao	16	1	6	14	88
14.	Cyprus	910	17	2	481	53
15.	Denmark	10,791	537	5	8959	83
16.	Diamond Princess	712	13	2	651	91
18.	Faeroe Islands	187		0	187	100
19.	Falkland Islands	13		0	13	100
20.	French Guiana	189	1	1	124	66
21.	French Polynesia	60		0	59	98
22.	Germany	175,699	8001	5	151,700	86
23.	Gibraltar	147		0	144	98
24.	Greenland	11		0	11	100
25.	Grenada	22		0	14	64
26.	Guadeloupe	155	13	8	109	70
27.	Hong Kong	1053	4	0	1019	97
28.	Iceland	1802	10	1	1782	99
29.	Isle of Man	334	24	7	285	85
30.	Italy	223,885	31,610	14	120,205	54
31.	Ivory Coast	2017	24	1	942	47
33.	Lebanon	891	26	3	246	28
34.	Liechtenstein	82	1	1	55	67
35.	Luxembourg	3923	104	3	3682	94
36.	Macao	45		0	43	96
37.	Martinique	192	14	7	91	47
38.	Mayotte	1210	16	1	627	52
40.	Montserrat	11	1	9	10	91
41.	MS Zaandam	9	2	22	7	78
42.	Netherlands	43,681	5643	13	N/A	#VALUE!
43.	New Caledonia	18		0	18	100
45.	Norway	8219	232	3	32	0
47.	Reunion	441		0	354	80
49.	Saint Martin	39	3	8	30	77
50.	Saint Pierre Miquelon	1		0	1	100
51.	San Marino	652	41	6	189	29
52.	Sint Maarten	76	15	20	46	61
53.	Spain	274,367	27,459	10	188,967	69
54.	St. Barth	6		0	6	100
55.	St. Vincent Grenadines	17		0	14	82
56.	Suriname	10	1	10	9	90
57.	Switzerland	30,514	1878	6	27,100	89
58.	Taiwan	440	7	2	387	88
59.	Trinidad and Tobago	116	8	7	107	92
60.	Turks and Caicos	12	1	8	10	83
61.	UK	236,711	33,998	14	N/A	#VALUE!
62.	USA	1,484,285	88,507	6	326,242	22

Table 1 (*Continued*)

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Deaths as %	Total Recovered Cases	Recovered cases as %
63.	Vatican City	12		0	2	17
64.	Western Sahara	6		0	6	100
	Total	2,593,955	204,012	8	882,176	34
	Average	44,723	4857	11	15,753	35

more severe COVID-19 infections and high mortality.[20] Five clinical trials have started in different countries using the BCG vaccine as a preventive treatment for the COVID-19 in Health Care Workers and the elderly population.[26] According to the available literature, the BCG vaccine might help in reducing the incidence of COVID-19 infections with less morbidity and mortality; BCG vaccine might be a game-changer in preventing the spread of the COVID-19 pandemic.

Safety of revaccination

Revaccination of BCG did not provide any extra protection against TB.[13] Control and prevention of tuberculosis provided guidelines that people who work in hospital settings regardless of age, those unvaccinated earlier, and those having Heaf grade 1 or negative on tuberculin testing, might be vaccinated for the BCG vaccine. The HCW were directly dealing with TB patients and did not have a BCG scar so revaccination might be recommended.[57,58] The BCG vaccine causes swelling at the site of vaccination. However, cross-reactions of BCG may occur in people with a compromised immune system and pregnant women, so extra protection could be provided to pregnant women and immune-compromised people before BCG vaccination.[13] A study has shown that after revaccination in students, the relative risk of adverse reactions with the scar was twice, as compared to without scar.[59] The researchers reported that the second dose of BCG or revaccination did not generally cause any adverse reactions - sometimes it can cause adverse reactions but these are very rare. The study reporting in American Indians and Alaskan natives BCG vaccination provided that the long-lasting potency and it has shown that a dose of BCG provides safety for 50–60 years.[60] The clinical trials also observed the same efficacy of the BCG vaccine in observational case-control studies, but unknown in the elderly population.[59] Another study performed on elderly guinea pigs revealed that the revaccination of the BCG-Tokyo vaccine against the infection reduced the replication of bacteria in the lungs, spleen, and alveolar lymph nodes.[61]

COVID-19 status in BCG implemented and non-implemented countries (May 16, 2020)

The preliminary studies have observed a correlation between countries which have universal policies of BCG vaccination for their citizens, showing fewer COVID-19 confirmed cases with a very low mortality rate.[10] Estimation of the correlation of BCG with the spread of COVID-19 infection in different countries started the clinical trials to determine whether the BCG vaccine provides any protection against the COVID-19 pandemic. Status of the coronavirus infection is shown in the tables with or without a universal BCG immunization program. Data of COVID-19 collected from the worldometer (https://www.worldometers.info/coronavirus/) and converted into the death percentage, percentage of recovered cases, and total infected cases in the form of BCG implemented countries status and non-implemented countries status. BCG vaccination data was collected country-wise from the BCG World Atlas Database site (Tables 1 and 2).

The average of the total number of COVID-19 cases was 44,723 in without BCG implemented countries, whereas

Table 2 SARS-CoV-2 infection in BCG implemented countries.

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Death % in total cases	Recovered Cases	Recovered cases as %
1.	Afghanistan	6053	153	2.527672229	745	12.30794647
2.	Albania	916	31	3.384279476	705	76.9650655
3.	Algeria	6629	536	8.085684115	3271	49.34379243
4.	Angola	761	2	0.262812089	17	2.23390276
5.	Argentina	7479	356	4.759994652	2497	33.38681642
6.	Armenia	4283	55	1.284146626	1791	41.81648377
7.	Austria	7037	98	1.392638909	6353	90.27994884
8.	Azerbaijan	2980	36	1.208053691	1886	63.2885906
9.	Bangladesh	20,995	314	1.495594189	4117	19.60943082
10.	Belarus	27,730	156	0.562567616	8807	31.7598269
11.	Belize	18	2	11.11111111	16	88.88888889
12.	Benin	339	2	0.589970501	83	24.48377581

Table 2 (*Continued*)

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Death % in total cases	Recovered Cases	Recovered cases as %
13.	Bhutan	21		0	5	23.80952381
14.	Bolivia (Plurinational State of)	3577	164	4.584847638	434	12.13307241
15.	Bosnia and Herzegovina	2236	128	5.72450805	1336	59.74955277
16.	Botswana	24	1	4.166666667	17	70.83333333
17.	Brazil	220,291	14,962	6.791925226	84,970	38.57170742
18.	Brunei Darussalam	141	1	0.709219858	136	96.45390071
19.	Bulgaria	2175	105	4.827586207	573	26.34482759
20.	Burkina Faso	780	51	6.538461538	595	76.28205128
21.	Burundi	15	1	6.666666667	7	46.66666667
22.	Cambodia	122		0	122	100
23.	Cameroon	3105	140	4.508856683	1567	50.46698873
24.	Cabo Verde	326	2	0.613496933	67	20.55214724
25.	Central African Republic	301		0	13	4.318936877
26.	Chad	428	48	11.21495327	88	20.56074766
27.	Chile	39,542	394	0.996408882	16,614	42.01608416
28.	China	82,941	4633	5.58589841	78,219	94.3067964
29.	Colombia	14,216	546	3.840742825	3460	24.33877321
30.	Comoros	11	1	9.090909091	3	27.27272727
31.	Congo	391	15	3.836317136	87	22.25063939
32.	Cook Islands	0	0	0	0	0
33.	Costa Rica	843	10	1.18623962	542	64.29418743
34.	Croatia	2222	95	4.275427543	1869	84.11341134
35.	Cuba	1840	79	4.293478261	1425	77.44565217
36.	Czechia	8404	295	3.510233222	5381	64.02903379
37.	Côte d'Ivoire	0	0	0	0	0
38.	Democratic People's Republic of Korea	0	0	0	0	0
40.	Djibouti	1309	4	0.305576776	935	71.42857143
41.	Dominica	16		0	15	93.75
42.	Dominican Republic	11,739	424	3.611891984	3557	30.30070704
43.	Ecuador	31,467	2594	8.243556742	3433	10.90984206
44.	Egypt	11,228	592	5.272532953	2799	24.92874955
45.	El Salvador	1265	25	1.976284585	441	34.86166008
46.	Equatorial Guinea	594	7	1.178451178	22	3.703703704
47.	Eritrea	39	0	0	39	100
48.	Estonia	1770	63	3.559322034	934	52.76836158
49.	Ethiopia	287	5	1.742160279	112	39.02439024
50.	Fiji	18	0	0	15	83.33333333
51.	Finland	6228	293	4.704560051	5000	80.28259473
52.	France	179,506	27,529	15.33597763	60,448	33.6746404
53.	Gabon	1209	10	0.827129859	219	18.11414392
54.	Gambia	23	1	4.347826087	12	52.17391304
55.	Georgia	677	12	1.772525849	419	61.89069424
56.	Ghana	5638	28	0.496630011	1460	25.8957077
57.	Greece	2810	160	5.693950178	1374	48.89679715
58.	Guatemala	1643	30	1.82592818	135	8.216676811
59.	Guinea	2531	15	0.592651126	1094	43.22402213

(*Continued*)

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Death % in total cases	Recovered Cases	Recovered cases as %
60.	Guinea-Bissau	913	3	0.328587076	26	2.847754655
61.	Guyana	116	10	8.620689655	43	37.06896552
62.	Haiti	310	20	6.451612903	29	9.35483871
63.	Honduras	2460	134	5.447154472	264	10.73170732
64.	Hungary	3474	448	12.89579735	1371	39.46459413
65.	India	86,508	2760	3.190456374	30,773	35.57243261
66.	Indonesia	17,025	1089	6.396475771	3911	22.97209985
67.	Iran (Islamic Republic of)	116,635	6902	5.917606207	91,836	78.73794316
68.	Iraq	3193	117	3.664265581	2089	65.4243658
69.	Ireland	23,956	1518	6.336617131	19,470	81.27400234
70.	Israel	16,606	267	1.607852583	12,820	77.20101168
71.	Jamaica	511	9	1.761252446	121	23.67906067
72.	Japan	16,203	713	4.400419675	10,338	63.80299944
73.	Jordan	596	9	1.510067114	401	67.28187919
74.	Kazakhstan	5850	34	0.581196581	2707	46.27350427
75.	Kenya	781	45	5.76184379	284	36.36363636
76.	Kiribati	0	0	0	0	0
77.	Kuwait	12,860	96	0.746500778	3640	28.30482115
78.	Kyrgyzstan	1117	14	1.253357207	783	70.09847807
79.	Lao People's Democratic Republic	19	0	0	14	73.68421053
80.	Latvia	997	19	1.905717151	662	66.39919759
81.	Lesotho	1	0	0	1	100
82.	Liberia	219	20	9.132420091	108	49.31506849
83.	Libya	64	3	4.6875	28	43.75
84.	Lithuania	1534	55	3.585397653	988	64.40677966
85.	Madagascar	238		0	112	47.05882353
86.	Malawi	63	3	4.761904762	24	38.0952381
87.	Malaysia	6872	113	1.6443539	5512	80.20954598
88.	Maldives	1031	4	0.387972842	49	4.752667313
89.	Mali	806	46	5.70719603	455	56.4516129
90.	Malta	532	6	1.127819549	458	86.09022556
91.	Marshall Islands	0	0	0	0	0
92.	Mauritania	29	3	10.34482759	7	24.13793103
93.	Mauritius	332	10	3.012048193	322	96.98795181
94.	Mexico	45,032	4767	10.58580565	30,451	67.62080298
95.	Micronesia (Federated States of)	0	0	0	0	0
96.	Monaco	96	4	4.166666667	87	90.625
97.	Mongolia	135		0	20	14.81481481
98.	Morocco	6652	190	2.856283824	3400	51.11244738
99.	Mozambique	119		0	42	35.29411765
100.	Myanmar	182	6	3.296703297	89	48.9010989
101.	Namibia	16		0	13	81.25
102.	Nauru	0	0	0	0	0
103.	Nepal	276		0	36	13.04347826
104.	Nicaragua	25	8	32	7	28
105.	Niger	885	51	5.762711864	684	77.28813559
106.	Nigeria	5450	171	3.137614679	1320	24.22018349
107.	Niue	0	0	0	0	0
108.	Oman	5029	20	0.397693378	1436	28.55438457
109.	Pakistan	38,799	834	2.149539937	10,880	28.04195984
110.	Panama	9268	266	2.870090634	6080	65.60207164

(*Continued*)

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Death % in total cases	Recovered Cases	Recovered cases as %
111.	Papua New Guinea	8	0	0	8	100
112.	Paraguay	759	11	1.449275362	193	25.42819499
113.	Peru	84,495	2392	2.830936742	27,147	32.12852832
114.	Philippines	12,305	817	6.639577408	2561	20.81267777
115.	Poland	18,184	912	5.015398152	7175	39.45776507
116.	Portugal	28,583	1190	4.163313858	3328	11.64328447
117.	Qatar	29,583	14	0.047324477	3546	11.98661393
118.	South Korea	11,037	262	2.373833469	9851	89.25432636
119.	Republic of Moldova	5745	202	3.516100957	2228	38.78154917
120.	Romania	16,437	1070	6.509703717	9370	57.00553629
121.	Russia	272,043	2537	0.932573159	63,166	23.21912345
122.	Rwanda	287	0	0	177	61.67247387
123.	Saint Kitts and Nevis	15	0	0	14	93.33333333
124.	Saint Lucia	18	0	0	18	100
125.	Saint Vincent and the Grenadines	0	0	0	0	0
126.	Samoa	0	0	0	0	0
127.	Sao Tome and Principe	235	7	2.978723404	4	1.70212766
128.	Saudi Arabia	49,176	292	0.593785586	21,869	44.4708801
129.	Senegal	2310	25	1.082251082	890	38.52813853
130.	Serbia	10,438	225	2.155585361	4301	41.20521173
131.	Seychelles	11	0	0	10	90.90909091
132.	Sierra Leone	447	27	6.040268456	97	21.70022371
133.	Singapore	27,356	21	0.076765609	7248	26.49510162
134.	Slovakia	1493	28	1.87541862	1151	77.09310114
135.	Slovenia	1465	103	7.030716724	279	19.0443686
136.	Solomon Islands	0	0	0	0	0
137.	Somalia	1284	53	4.127725857	135	10.51401869
138.	South Africa	13,524	247	1.826382727	6083	44.97929607
139.	Sri Lanka	935	9	0.962566845	520	55.61497326
140.	Sudan	1964	91	4.633401222	205	10.43788187
141.	Eswatini	190	2	1.052631579	66	34.73684211
142.	Sweden	29,207	3646	12.4833088	4971	17.01989249
143.	Syrian Arab Republic	50	3	6	36	72
144.	Tajikistan	1118	33	2.951699463	0	0
145.	Thailand	3025	56	1.851239669	2855	94.38016529
146.	Republic of North Macedonia	1740	97	5.574712644	1251	71.89655172
147.	Timor-Leste	24	0	0	24	100
148.	Togo	263	11	4.182509506	96	36.50190114
149.	Tonga	0	0	0	0	0
150.	Tunisia	1035	45	4.347826087	802	77.48792271
151.	Turkey	146,457	4055	2.768730754	106,133	72.46700397
152.	Turkmenistan	0	0	0	0	0
153.	Tuvalu	0	0	0	0	0
154.	Uganda	203	0	0	63	31.03448276
155.	Ukraine	17,858	497	2.783066413	4906	27.47228133
156.	United Arab Emirates	21,831	210	0.961934863	7328	33.56694609

(*Continued*)

Sr. No.	Countries	COVID-19 Infected Cases	Total Deaths	Death % in total cases	Recovered Cases	Recovered cases as %
157.	United Republic of Tanzania	509	21	4.125736739	183	35.95284872
158.	Uruguay	732	19	2.595628415	553	75.54644809
159.	Uzbekistan	2691	11	0.408769974	2158	80.19323671
160.	Vanuatu	0	0	0	0	0
161.	Venezuela (Bolivarian Republic of)	459	10	2.178649237	229	49.89106754
162.	Vietnam	314	0	0	260	82.80254777
163.	Yemen	106	15	14.1509434	1	0.943396226
164.	Zambia	668	7	1.047904192	152	22.75449102
165.	Zimbabwe	42	4	9.523809524	13	30.95238095
166.	Montenegro	324	9	2.777777778	311	95.98765432
167.	South Sudan	236	4	1.694915254	4	1.694915254
	Total	1,981,967	95,277	4.807194065	858,437	43.31237604
	Average	11940.98193	606.8853503	5.082373912	5171.331325	43.30742109

implemented countries have a very lower average of infected cases 11940.98. BCG implemented countries have fewer deaths percentage, around 5.08%, as compared to the 11% in without implemented countries. Moreover, the recovered cases percentage was also high in BCG implemented countries, around 43%, whereas in without implemented countries it was 35%.

Conclusion

The SARS-Cov-2 pandemic is spreading rapidly and the entire world under the grip of this severe pulmonary disease. The countries are fighting this pandemic with their ability but developed countries such as the USA, Italy, Spain, UK, etc., have been badly affected. People of these countries have a low immune response against any type of infection like COVID-19 because these countries have no universal immunization program or it was removed by the government at an earlier time. Other countries such as India, Afghanistan, Nepal, Bhutan, China, Pakistan, Bangladesh, etc. have universal immunization programs like the BCG vaccination program. The BCG vaccine has the potential to activate the immune response against the viral infection. The severity of the COVID-19 pandemic is very low with a slower spread in those countries that have the universal BCG immunization program. Australia, Germany, USA, etc., started the clinical trial of the BCG vaccine in Health Care Workers and the Elderly Population to prevent the infection of COVID-19. The correlation of BCG vaccination with COVID-19 has shown fewer confirmed cases with low mortality and a high recovered rate in universal BCG immunization countries. Table 1 contains the data of BCG unimplemented countries, and Table 2 contains the data of universal BCG implemented countries. Several new vaccines are being developed by different companies and clinical trials have started, until approval or success of any clinical trial for the specific vaccine of COVID-19 the BCG vaccine might be used as a preventive treatment for the COVID-19 pandemic.

Conflicts of interest

The authors declare that they have no conflict of interest.

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