Relationship between COVID-19 death toll doubling time and national BCG vaccination policy

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Abstract

In this manuscript, we showed a statistically significant difference of the doubling times of the death toll between the group of countries with national universal Bacillus Calmette-Guerin (BCG) vaccination and the group without it for recent years. Based on a statistical test, the distributions of the doubling time of these two groups were significantly different (p=0.007). Miller et al. reported the relationship between BCG vaccination and mortality for COVID-19 based on deaths per million inhabitants. However, they did not take into account the differences in COVID-19 detection rates among the countries and the epidemic stages of the countries. Therefore we used a doubling time of the death toll as a more stable indicator instead. We also investigated the dependency of the BCG strains. Among the 42 BCG-vaccinated countries, the median doubling time of the eight countries using "Tokyo 172-1" strain at least partially (Japan, Iraq, Malaysia, South Korea, Philippines, Saudi Arabia, Pakistan, and Bangladesh) was 7.2 days, and that of the other 34 vaccinated countries was 5.5 days. Their distributions were also significantly different (p=0.026).

The non-specific effects of Bacillus Calmette-Guerin (BCG) vaccination have been enthusiastically discussed.[1] Miller et al. reported the relationship between BCG vaccination and mortality for COVID-19 based on deaths per million inhabitants.[2] However they did not take into account the differences in COVID-19 detection rates among the countries and the epidemic stages of the countries. Therefore we used a doubling time (DT) of the death toll as a more stable indicator.

First, we investigated the DT of COVID-19 deaths in 57 countries (source: Our World in Data,[3] as of 20 April 2020). We defined the baseline date of each country as the date when summed fatalities of at least ten people was first observed in the country. We covered all countries that have at least 10-day observation period and had a population[4] of more than 1 million. To exclude the effect of social interventions, the death toll data of the country was truncated by 30 days after the baseline date (for 20 countries among 57).

Next, we surveyed the national BCG vaccination policies of each country (sources: BCG Atlas,[5] WHO-UNICEF report,[6] and other 20 papers[7-26]). The 57 countries were divided into two groups based on whether the majority of the population between the ages of 0 and 39 was vaccinated ("BCG") or not ("non-BCG"). BCG vaccination records, especially cover rates, are reliable only for the last few decades for several countries. The BCG policy data collected as well as calculated DTs for 57 countries are shown in Table 1.

Figure 1 shows the distributions of DTs. Most of DTs for 42 "BCG" countries are longer than 15 "non-BCG" countries (the medians of the DTs are 5.6 days and 4.2 days, respectively.) The variance of DTs of "BCG" countries was almost same as that of "non-BCG" ($\sigma = 1.7$ and $\sigma = 1.8$, respectively.) Based on a Wilcoxson rank-sum test, the distributions of these two groups were significantly different at the significance level of 0.05 ($p = 0.007$).

We also investigated the dependency of the BCG strains (Figure 2). Among the 42 "BCG" countries, the median DT of the eight countries using "Tokyo 172-1" strain at least partially (Japan, Iraq, Malaysia, South Korea, Philippines, Saudi Arabia, Pakistan, and Bangladesh) was 7.2 days, and that of the other 34 vaccinated countries was 5.5 days. The variance of DTs of "Tokyo 172-1" countries was large ($\sigma = 2.4$) while DTs of "other BCG strains" are relatively concentrated ($\sigma = 1.3$). Their distributions were also significantly different at the significance level of 0.05 ($p = 0.026$).

We showed a statistically significant difference of the doubling times of the death toll between "BCG" and "non-BCG" countries. However, the correlation might be spurious and does not directly imply causality. In addition, we should carefully take the suggested difference between BCG strains, because the number of samples are not enough and some countries are using mixed strains.

The raw data version (an excel file) of Table 1 is available at http://www.bi.cs.titech.ac.jp/COVID-19/Death_vs_BCGpolicy.html.

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Authors' contributions:

Y.A. designed the study, and performed literature search, data table compilation, and basic data analysis. T.I. performed the statistical tests, and made figures. Y.A. and T.I. wrote the manuscript.

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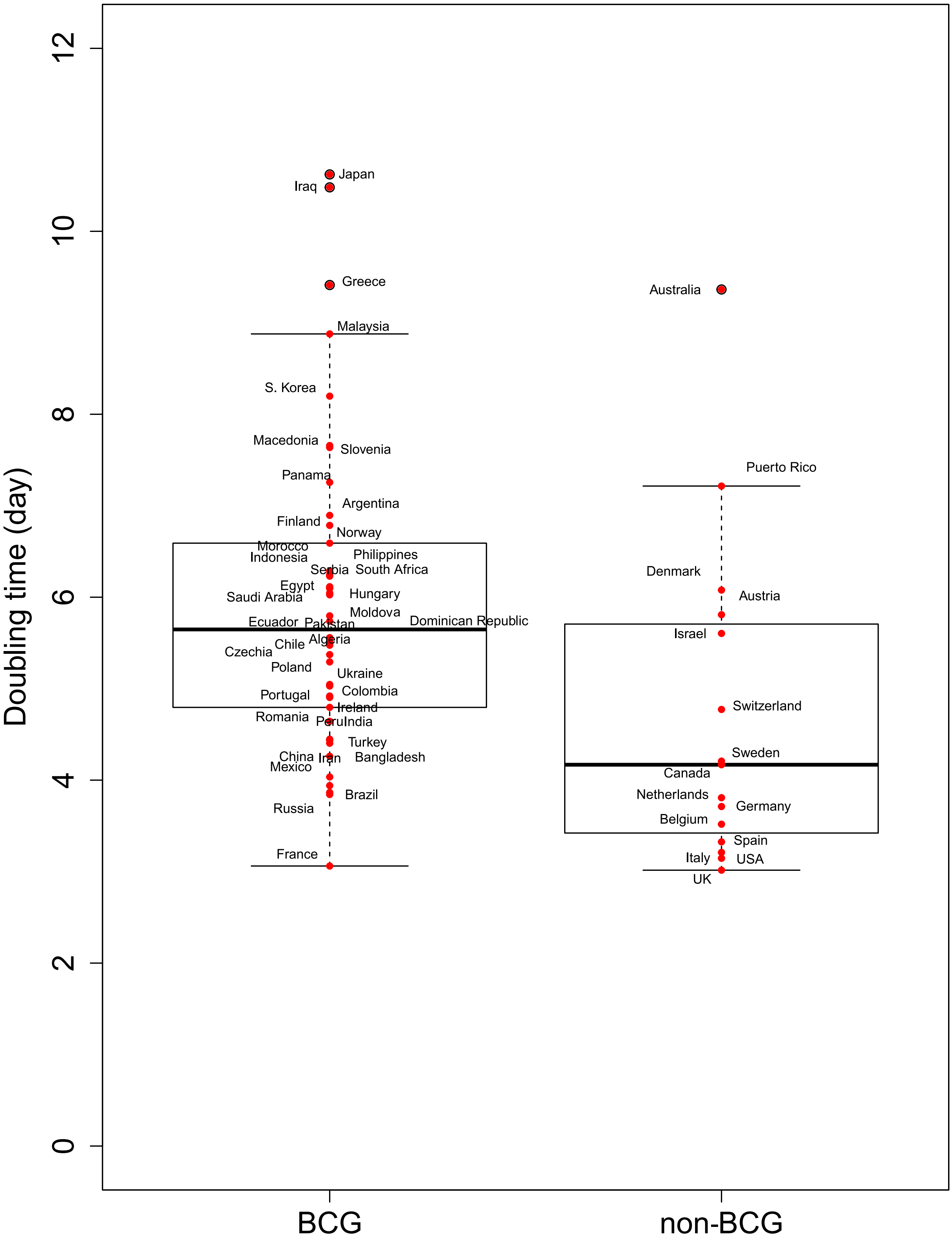

Figure 1. The death toll doubling time (DT) of BCG vaccinated ("BCG") and non-vaccinated ("non-BCG") countries

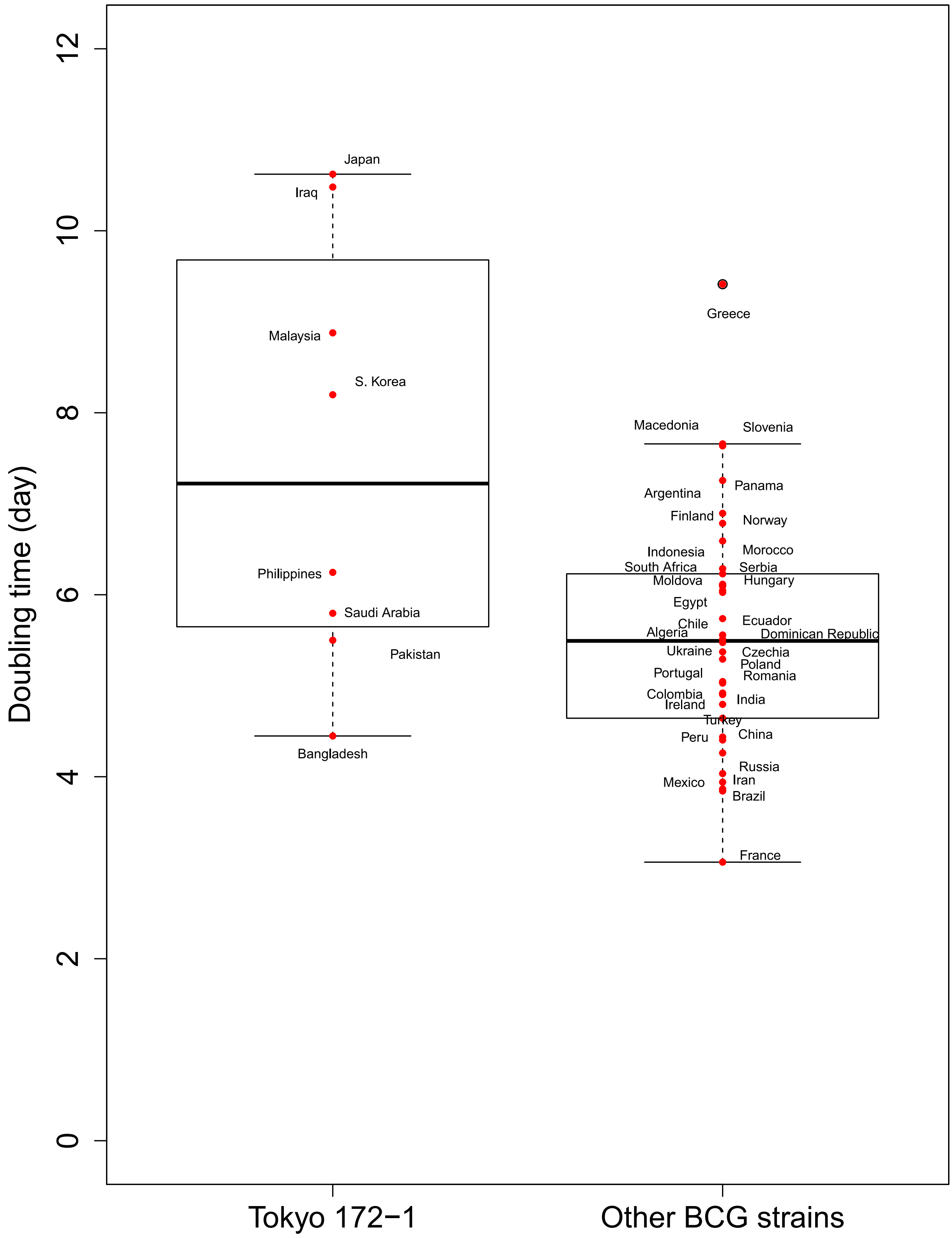

Figure 2. The death toll doubling time (DT) of Tokyo 172-1 ("Tokyo 172-1") and other BCG strains ("Other BCG strains") countries

Table 1. The COVID-19 death toll doubling time and the national BCG vaccination policy of 57 countries

	Country	Population at 2020 estimated (K)	Period start	Total death as of the day: D0	Period end	Total death as of the day: D1	Period length P (day)	Growth ratio: R	Doubling time (day)	BCG mass vaccination years	Timing of 1st BCG	Vaccinated age at 2020	Most of 0-39 y/o are vaccinated	BCG strains	Tokyo172-1 strain is used at least partially	BCG policy References
		[4], min 1M	death >= 10	[3]		[3]	min 10 max 30	= D1/D0	= P/log2(R)					[5][22][23][24][25][26]		
1	**UK**	67,886	13-Mar	10	12-Apr	9,875	30	987.5	**3.0**	1953-2005	12-13 y/o	28-80	**No**	Glaxo		[5][7]
2	**France**	65,274	8-Mar	10	7-Apr	8,911	30	891.1	**3.1**	1950-2007	at Birth ?	13-70	**Yes**	Danish 1331	**No**	[5][6][7]
3	**Italy**	60,462	26-Feb	11	27-Mar	8,165	30	742.3	**3.1**	Limited			**No**	Danish 1331		[5]
4	**USA**	331,003	5-Mar	11	4-Apr	7,157	30	650.6	**3.2**	Limited			**No**			[5][7]
5	**Spain**	46,755	10-Mar	28	9-Apr	14,555	30	519.8	**3.3**	1965-1981	at Birth	39-55	**No**	Danish 1331		[5][7]
6	**Belgium**	11,590	19-Mar	14	18-Apr	5,163	30	368.8	**3.5**	Limited			**No**	Pasteur 1173		[5][7]
7	**Germany**	83,784	16-Mar	12	15-Apr	3,254	30	271.2	**3.7**	1961-1998	at Birth	22-59	**No**	Danish 1331		[5][7]
8	**Netherlands**	17,135	15-Mar	12	14-Apr	2,823	30	235.3	**3.8**	Limited			**No**	Bulgaria		[5][7]
9	**Brazil**	212,559	21-Mar	11	20-Apr	2,462	30	223.8	**3.8**	<1990-2018+	at Birth	0-30+	**Yes**	Moreau	**No**	[5][6][7]
10	**Russia**	145,934	31-Mar	10	20-Apr	361	20	36.1	**3.9**	<1992-2018+	at Birth	0-28+	**Yes**	Russia	**No**	[5][6][7]
11	**Mexico**	128,933	28-Mar	12	20-Apr	686	23	57.2	**3.9**	1951-2018+	at Birth	0-69	**Yes**	Danish 1331	**No**	[5][6]
12	**Iran**	83,993	25-Feb	12	26-Mar	2,077	30	173.1	**4.0**	<1990-2018+	at Birth	0-30+	**Yes**	Pasteur 1173 P2	**No**	[5][6][7]
13	**Canada**	37,742	20-Mar	10	19-Apr	1,467	30	146.7	**4.2**	Limited			**No**	Connaught (until 2012), Tokyo 172-1 (from 2012) [5]		[5][7]
14	**Sweden**	10,099	19-Mar	10	18-Apr	1,400	30	140.0	**4.2**	1940-1975	at Birth	45-80	**No**	Danish 1331		[5][6][7]
15	**China**	1,439,324	22-Jan	17	21-Feb	2,238	30	131.6	**4.3**	1949-2018+	at Birth	0-71	**Yes**	Shanghai D2PB302	**No**	[5][6][10]
16	**Turkey**	84,339	22-Mar	21	20-Apr	2,017	29	96.0	**4.4**	1952-2018+	at Birth	0-68	**Yes**	Serum Inst. India (Russia)	**No**	[5][6]
17	**Peru**	32,972	28-Mar	11	20-Apr	400	23	36.4	**4.4**	<1990-2018+	at Birth	0-30+	**Yes**	Danish 1331	**No**	[5][6]
18	**Bangladesh**	164,689	7-Apr	12	20-Apr	91	13	7.6	**4.4**	<1990-2018+	at Birth	0-30+	**Yes**	Serum Inst. India (Russia) [5], Tokyo 172-1 [11]	**Yes**	[5][6][11]
19	**India**	1,380,004	26-Mar	13	20-Apr	543	25	41.8	**4.6**	1951-2018+	at Birth	0-69	**Yes**	Danish 1331	**No**	[5][6][7][12]
20	**Switzerland**	8,655	15-Mar	11	14-Apr	858	30	78.0	**4.8**	1960s-1987	at Birth	33-50+	**No**	Merieux (Danish)		[5]
21	**Ireland**	4,938	27-Mar	19	20-Apr	610	24	32.1	**4.8**	1950s-2003?	at Birth	17-60+	**Yes**	Danish 1331	**No**	[5][6][7][13]
22	**Romania**	19,238	25-Mar	11	20-Apr	434	26	39.5	**4.9**	1928-2018+	at Birth	0-92	**Yes**	Romanian BCG substrain Catacuzino Institute	**No**	[5][6][7]
23	**Portugal**	10,197	22-Mar	12	20-Apr	714	29	59.5	**4.9**	1965-2015	at Birth	5-55	**Yes**	Danish 1331	**No**	[5][6][7][8][14]
24	**Poland**	37,847	25-Mar	10	20-Apr	360	26	36.0	**5.0**	1955-2018+	at Birth	0-65	**Yes**	Danish 1331	**No**	[5][6][7]
25	**Colombia**	50,883	30-Mar	10	20-Apr	179	21	17.9	**5.0**	<1980-2018+	at Birth	0-40+	**Yes**	Pasteur 1173	**No**	[5][6]
26	**Ukraine**	43,734	31-Mar	11	20-Apr	151	20	13.7	**5.3**	<1992-2018+	at Birth	0-28+	**Yes**	Bulgaria NCIPD	**No**	[5][6]
27	**Czechia**	10,709	29-Mar	11	20-Apr	188	22	17.1	**5.4**	1953-2010	at Birth	10-67	**Yes**	Moreau	**No**	[5][6][7]
28	**Chile**	19,116	1-Apr	12	20-Apr	133	19	11.1	**5.5**	<1980-2018+	at Birth	0-40+	**Yes**	Danish 1331	**No**	[5][6]
29	**Pakistan**	220,892	29-Mar	11	20-Apr	176	22	16.0	**5.5**	1978-2018+	at Birth	0-42	**Yes**	Danish 1331 (until 2007), Tokyo 172-1 (from 2008) [5][11]	**Yes**	[5][6][7][11]
30	**Ecuador**	17,643	23-Mar	14	20-Apr	474	28	33.9	**5.5**	<1995-2018+	at Birth	0-25+	**Yes**	Russia/Bulgaria	**No**	[5][6]
31	**Dominican Republic**	10,848	26-Mar	10	20-Apr	226	25	22.6	**5.6**	<1990-2018+	at Birth	0-30+	**Yes**	Russia/Bulgaria	**No**	[5][6]
32	**Israel**	8,656	28-Mar	10	20-Apr	172	23	17.2	**5.6**	1955-1982	at Birth	38-65	**No**			[5][6][7]
33	**Algeria**	43,851	21-Mar	10	20-Apr	375	30	37.5	**5.7**	<1985-2018+	at Birth	0-35+	**Yes**		**Unknown**	[5][6]
34	**Saudi Arabia**	34,814	1-Apr	10	20-Apr	97	19	9.7	**5.8**	<1985-2018+	at Birth	0-35+	**Yes**	Pasteur [5], Danish 1331 [15], Tokyo 172-1 [11]	**Yes**	[5][6][11][15]
35	**Austria**	9,006	23-Mar	16	20-Apr	452	28	28.3	**5.8**	1952-1990	at Birth	30-68	**No**			[5][6][7]
36	**Hungary**	9,660	25-Mar	10	20-Apr	199	26	19.9	**6.0**	1953-2018+	at Birth	0-67	**Yes**	Danish 1331	**No**	[5][6][7]
37	**Moldova**	4,034	5-Apr	12	20-Apr	67	15	5.6	**6.0**	<1992-2018+	at Birth	0-28+	**Yes**		**Unknown**	[5][6]
38	**Denmark**	5,792	22-Mar	13	20-Apr	355	29	27.3	**6.1**	1946-1986	at Birth	34-74	**No**	Danish 1331		[5][7]
39	**Serbia**	8,737	29-Mar	10	20-Apr	122	22	12.2	**6.1**	<1992-2018+	at Birth	0-28+	**Yes**	Pasteur 1173 P2	**No**	[6][7][16]
40	**South Africa**	59,309	6-Apr	11	20-Apr	54	14	4.9	**6.1**	<1995-2011+	at Birth	0-25+	**Yes**	Danish 1331	**No**	[5][6][7]
41	**Egypt**	102,334	23-Mar	10	20-Apr	239	28	23.9	**6.1**	<1990-2018+	at Birth	0-30+	**Yes**		**Unknown**	[5][6]
42	**Indonesia**	273,524	20-Mar	19	19-Apr	535	30	28.2	**6.2**	<1990-2018+	at Birth	0-30+	**Yes**	Pasteur 1173	**No**	[5][6]
43	**Philippines**	109,581	16-Mar	12	15-Apr	335	30	27.9	**6.2**	1979-2018+	at Birth	0-41	**Yes**	Tokyo 172-1, and others? (hearing from Japan BCG Lab.)	**Yes**	[5][6][7]
44	**Morocco**	36,911	27-Mar	10	20-Apr	141	24	14.1	**6.3**	1949-2018+	at Birth	0-71	**Yes**		**Unknown**	[5][6][7][17]
45	**Norway**	5,421	25-Mar	10	20-Apr	154	26	15.4	**6.6**	1947-2009	at Birth	11-73	**Yes**	Danish 1331	**No**	[5][7]
46	**Finland**	5,541	30-Mar	11	20-Apr	94	21	8.5	**6.8**	1941-2006	at Birth	14-79	**Yes**	Glaxo, Danish 1331	**No**	[5][6][7]
47	**Argentina**	45,196	27-Mar	12	20-Apr	134	24	11.2	**6.9**	<1985-2018+	at Birth	0-35+	**Yes**	Anlis Malbran (Pasteur)	**No**	[5][6]
48	**Puerto Rico**	2,861	2-Apr	11	20-Apr	62	18	5.6	**7.2**	Limited?			**No**			[18]
49	**Panama**	4,315	28-Mar	14	20-Apr	126	23	9.0	**7.3**	<1980-2018+	at Birth	0-40+	**Yes**	Russia/Bulgaria	**No**	[5][6][19]
50	**Slovenia**	2,079	30-Mar	11	20-Apr	74	21	6.7	**7.6**	1947-2005	at Birth	15-73	**Yes**	Danish 1331	**No**	[5][6]
51	**Macedonia**	2,083	2-Apr	10	20-Apr	51	18	5.1	**7.7**	<1993-2018+	at Birth	0-27+	**Yes**	Tronto Canada (Connaught)	**No**	[5][6]
52	**S. Korea**	51,269	26-Feb	11	27-Mar	139	30	12.6	**8.2**	1970s-2018+	at Birth	0-40+	**Yes**	Tokyo 172-1 [11][25], Danish [5]	**Yes**	[5][6][7][11][25]
53	**Malaysia**	32,366	23-Mar	10	20-Apr	89	28	8.9	**8.9**	<1980-2018+	at Birth	0-40+	**Yes**	Tokyo 172-1 [20]	**Yes**	[5][6][7][20]
54	**Australia**	25,500	26-Mar	11	20-Apr	70	25	6.4	**9.4**	1950s-1985?	school age	40-70	**No**	Connaught (until 2010s)		[5][7]
55	**Greece**	10,423	22-Mar	13	20-Apr	110	29	8.5	**9.4**	<1980-2014+	6 y/o	12-46+	**Yes**	Danish 1331	**No**	[5][6][7][21]
56	**Iraq**	40,223	18-Mar	11	17-Apr	80	30	7.3	**10.5**	<1980-2018+	at Birth	0-40+	**Yes**	Tokyo 172-1 [26]	**Yes**	[5][6]
57	**Japan**	126,476	11-Mar	12	10-Apr	85	30	7.1	**10.6**	<1951-2020	at Birth	0-69+	**Yes**	Tokyo 172-1 [11][25]	**Yes**	[5][6][7][11][25]
													p = 0.007 Wilcoxon rank sum test		**p = 0.026** Wilcoxon rank sum test	