



# Recommending a Patient-Level Study to Confirm that BCG Vaccination Accounts for the Relatively Low COVID-19 Mortality Rate in the Philippines

Medical researchers have pointed out wide differences in COVID-related death rates among countries; and several explanations have been offered such as the high number of old people in a country, number of tourists, number of immigrants, geographic location and climate, size of the population, etc. One possible explanation that deserves further study is that countries where the COVID death rate is low are those countries where mass BCG vaccination is in place, such as the Philippines. Indeed, compared to countries who have never had mass BCG vaccination, i.e. USA, Canada, Italy, Netherlands and Belgium, the death rate due to COVID 19 in the Philippines is 16 to 131 times lower. The difference is also quite large compared to those countries where there had been mass BCG vaccination in the past but had been discontinued since 2 to 4 decades.

## Policy Recommendation

Using the well-known *Mantoux screening test* (also referred to as **Mantoux test or Mendel–Mantoux test, tuberculin sensitivity test, or PPD test**), conduct a patient-level study to determine whether (1) there is a disproportionately high percentage of people with the antibodies against *M. tuberculosis* among those who test negative for COVID-19; and (2) there is a disproportionately low percentage of people with the antibodies against *M. tuberculosis* among those who are or have been in the ICU as severe positive cases of COVID 19.

If the presence of the antibodies to combat pulmonary tuberculosis can lower the infection rate or reduce the severity of COVID-19, then the Philippines can consider a program for mass BCG (re)vaccination among those who test negative on the Mantoux Test, except for individuals whose specific medical case would put them more at risk if vaccinated with the BCG vaccine.

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## Introduction

Compared to the Philippines, the number of COVID-19-related deaths is much higher in Western Europe and North America. One pattern that has been reported in newspaper reports and journal papers awaiting successful peer review (Hegarty, Kamat, Zafirakis, & Dinardo, 2020; Yu, 2020; Dayal & Gupta, 2020; UMC Utrecht, 2020; Murdoch Childrens Research Institute, 2020) is that, indeed, the fatality rate due to COVID-19 is significantly higher in countries where there has not been any mass BCG vaccination (e.g., U.S.A., Canada, Italy, Netherlands, and Belgium) or where there had been mass BCG vaccination in the past but were discontinued (e.g., U.K., Spain, France, Germany, Sweden, Denmark, Finland, Norway, Luxemburg, Switzerland, Austria, Ecuador, Australia, and New Zealand).

## Focus on the Philippines

To compare the fatality rate of COVID-19 in the Philippines with that of other countries in ASEAN, East Asia, Oceania, Western Europe, North America, and some countries of Latin America, we use the cumulative number of *deaths per million* inhabitants (DPM) based on reported death counts from the Johns Hopkins University Corona Virus Resource Center (<https://coronavirus.jhu.edu/map.html>).

Table 1 shows that the DPM in the Philippines is estimated to be four as of April 22, and five as of April 28. This rate is more or less the same among countries in the ASEAN region. Comparing the DPM of the Philippines to those countries who have never had a mass BCG vaccination, the DPM in the Philippines is 16 to 131 times lower. Except for Australia and New Zealand, the DPM of the Philippines is 7 to 105 times lower than that of any of the countries in Western Europe that have discontinued mass BCG vaccination. Note that Greece and Poland have much lower DPM, and these two European countries have a mass BCG vaccination in place. Note also that Ecuador, the only country in Latin America that has discontinued its mass BCG vaccination program, has a much higher DPM than the other countries in Latin America.

We also calculated the number of *deaths per million of inhabitants among the urban population* and the same very huge differences can be noticed when comparing among countries that have or do not have a mass BCG vaccination in place. Note that the 2020 population figures of each of the 36 countries, as well as their urbanization index, were taken from WorldOMeters (<https://www.worldometers.info/world-population/population-by-country/>).

It should be emphasized, however, that “mass BCG vaccination” cannot account for the big difference between the DPM in Sweden compared to the other Scandinavian countries. Nor does it explain the large difference between the relatively low rate in Canada (75) compared to that of the U.S.A. (170). It also does not explain why Australia and New Zealand have more or less the same DPM as the Philippines, despite having discontinued mass BCG vaccination. Among the countries with mass BCG vaccination in place, there are two that stand out: Portugal (93) and Ireland (223).

Of course, it is possible that Australia and New Zealand may have had a huge influx of immigrants from Asia who have been vaccinated in the countries where they came from. As for Portugal and Ireland, their DPM indices are far lower than those of neighbor Spain and the U.K./France, respectively.

## Patient-Level Study

Instead of looking at macro-level figures, it would be best to study the correlation at the patient level and to do this for the specific case of the Philippines. It would be useful to study the correlation using a more specific independent variable—the presence of the *M. tuberculosis antigen*—which is a marker for the antibody response against pulmonary tuberculosis (TB). Indeed, the Philippines continues to mandate (mass) BCG vaccination among all young infants. However, the vaccine would normally be effective for about 15-18 years only. Older people, therefore, unless they have been exposed to TB, would lose immunity to TB by the time they become adults. The Philippines, however, is classified among those countries in the world where the TB burden is high, along with other ASEAN countries such as Thailand and Indonesia. Thus, the Filipino people, especially those in the urban, high density, lower-income communities, may have a high chance of being “regularly” exposed to TB cases, and hence might have a high chance of continually having the TB antigen.

Riding on the recently intensified mass-testing for COVID-19, it is useful and timely to subject a randomly selected group of asymptomatic persons to the Mantoux Test. Those who test negative for COVID-19 will be in Group I, whereas those who test positive but are asymptomatic or have mild symptoms will be in Group II. Also, all patients admitted in participating hospitals may be given the Mantoux Test, and those who end up in the ICU are all included in Group III.

We assume standard testing and research procedures, such as ensuring informed consent and considering the medical condition of the human subject before performing the Mantoux Test. Note that there is a similar confirmatory test that is being proposed for India (Sruthijith, K. K. & Kamat, 2020).

The specific, targeted study that zeroes in on actual COVID-19 patients would confirm what is observed at the macro level. If the COVID-19 virus has disproportionately infected those without the BCG-related antigen or has made their infection more likely to be severe or critical, then it will provide enough basis to re-vaccinate selected high-risk groups, such as healthcare workers, without waiting for a COVID-19 vaccine. Alternately, depending on the results, it may even be enough basis to re-vaccinate anyone who does not carry the TB antigen.

## Conclusion

The BCG vaccine, being among the oldest vaccines that is still being used today, has been studied in great detail for many years now. Several epidemiological studies have shown that the BCG vaccine can lead to the production of antibodies that not only protect against *TB meningitis*, as well as adult *pulmonary tuberculosis* but also *asthma*, *leprosy*, and possibly *malaria* (Luca & Mihaescu, 2013; SAGE Working Group on BCG Vaccines & WHO Secretariat, 2017). Indeed, there are clinical trials underway in Australia to vaccinate with BCG all healthcare workers (UMC Utrecht, 2020; Murdoch Childrens Research Institute, 2020). On the other hand, there are also cautionary briefs and rapid review from WHO and Oxford University (Soliman, Brassey, Plüddemann, & Heneghan, 2020; World Health Organization, 2020) that would call for additional epidemiological studies to confirm what may be only “gleaned” from macro-level correlation studies.

The report by the SAGE Working Group on BCG Vaccines and WHO Secretariat (2017) provides an insight to the non-specific immunological effects (NSIE) of the BCG vaccine:

A plethora of data from animal studies provide strong evidence for BCG’s ability to protect against a wide range of infections other than TB, including bacteria (e.g., *Shigella flexneri*), viruses (e.g., vaccinia virus) and protozoa (e.g., malaria). . . . . There are several plausible mechanisms for the NSIE of BCG and other vaccines (recently reviewed by Goodridge et al.). It is likely that the NSIE of BCG are mediated partly by heterologous effects on adaptive immunity, but also by potentiating innate immune responses through epigenetic mechanisms, a process termed ‘trained immunity.’ (p. 45)

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**Table 1. Death Statistics of 36 Countries. DPM is the Number of Deaths per Million Inhabitants, and DPMU is the Number of Deaths per Million Inhabitants Among the Urban Population**

	Population	Urban Population	Deaths	DPM	DPMU	Deaths	DPM	DPMU
			28-Apr			22-Apr		
Mass BCG Vaccination in place								
Ireland	4,937,786	3,110,805	1,102	223	354	730	148	235
Portugal	10,196,709	6,729,828	948	93	141	785	77	117
Hungary	9,660,351	6,955,453	291	30	42	225	23	32
Brazil	212,559,417	187,052,287	4,603	22	25	2,769	13	15
Poland	37,846,611	22,707,967	570	15	25	404	11	18
Greece	10,423,054	8,859,596	136	13	15	121	12	14
Mexico	128,932,753	108,303,513	1,434	11	13	857	7	8
Philippines	109,581,078	51,503,107	530	5	10	446	4	9
S Korea	51,269,185	42,040,732	244	5	6	238	5	6
Colombia	50,882,891	40,706,313	253	5	6	196	4	5
Argentina	45,195,774	42,032,070	197	4	5	151	3	4
Indonesia	273,523,615	153,173,224	773	3	5	635	2	4
Malaysia	32,365,999	25,245,479	100	3	4	93	3	4
Singapore	5,850,342	5,850,342	14	2	2	11	2	2
Thailand	69,799,978	35,597,989	54	1	2	49	1	1
Taiwan	23,816,775	18,815,252	6	0	0	6	0	0
Japan	126,476,461	116,358,344	385	3	3	281		2
Mass BCG Vaccination has been Discontinued								
Spain	46,754,778	37,403,822	23,822	510	637	21,717	464	581
France	65,273,511	53,524,279	23,327	357	436	20,829	319	389
UK	67,886,011	56,345,389	21,158	312	376	17,378	256	308
Sweden	10,099,265	8,887,353	2,355	233	265	1,937	192	218
Switzerland	8,654,622	6,404,420	1,685	195	263	1,478	171	231
Luxemburg	625,978	625,978	88	141	141	78	125	125
Denmark	5,792,202	5,097,138	434	75	85	384	66	75
Germany	83,783,942	63,675,796	6,136	73	96	4,862	58	76
Austria	9,006,398	5,133,647	569	63	111	510	57	99
Norway	5,421,241	4,499,630	206	38	46	182	34	40
Ecuador	17,643,054	11,115,124	663	38	60	520	29	47
Finland	5,540,720	4,765,019	199	36	42	149	27	31
Australia	25,499,884	21,929,900	83	3	4	67	3	3
New Zealand	4,822,233	4,195,343	19	4	5	14	3	3
Never had Mass BCG Vaccination								
Italy	60,461,826	41,718,660	26,977	446	647	24,648	408	591
Belgium	11,589,623	11,357,831	7,331	633	645	6,262	540	551
Netherlands	17,134,872	15,764,082	4,582	267	291	4,067	237	258
USA	331,002,651	274,732,200	56,386	170	205	45,075	136	164
Canada	37,742,154	30,571,145	2,841	75	93	1,915	51	63
All 36 Countries	1,565,754,909	1,158,498,464	190,501	94	164	160,069	79	138

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