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Higher BCG-induced trained immunity prevalence predicts protection from COVID-19: Implications for ongoing BCG trials

Samer Singh ¹ Dhiraj Kisho	re ² Rakesh K. Singh ³	Chandramani Pathak ⁴
Kishu Ranjan ⁵		

¹Centre of Experimental Medicine & Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

²Department of General Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

³Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh, India

⁴Amity Institute of Biotechnology, Amity University, Gurgaon, Haryana, India

⁵Department of Pathology, School of Medicine, Yale University, New Haven, Connecticut, USA

Correspondence

Samer Singh, Centre of Experimental Medicine & Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, 221005, Uttar Pradesh, India. Email: samer.singh10@bhu.ac.in

Rakesh K. Singh, Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, 221005, India. Email: rakesh_bc@bhu.ac.in

Kishu Ranjan, Department of Pathology, School of Medicine, Yale University, New Haven, CT 06519, USA. Email: kishu.ranjan@yale.edu

Abstract

Endeavors to identify potentially protective variables for COVID-19 impact on certain populations have remained a priority. Multiple attempts have been made to attribute the reduced COVID-19 impact on populations to their Bacillus-Calmette-Guérin (BCG) vaccination coverage ignoring the fact that the effect of childhood BCG vaccination wanes within 5 years while most of the COVID-19 cases and deaths have occurred in aged with comorbidities. Since the supposed protection being investigated could come from heterologous 'trained immunity' (TI) conferred by exposure to *Mycobacterium* spp. (i.e., environmental and BCG), it is argued that the estimates of the prevalence of TI in populations currently available as latent tuberculosis infection (LTBI) prevalence would be a better variable to evaluate such assertions. Indeed, when we analyze the European populations (24), and erstwhile East and West Germany populations completely disregarding their BCG vaccination coverage, the populations with higher TI prevalence consistently display reduced COVID-19 impact as compared to their lower TI prevalence neighbors. The TI estimates of the populations not the BCG coverage per se, negatively correlated with pandemic phase-matched COVID-19 incidences (r(24): -0.79 to -0.57; p-value < .004), mortality (r(24): -0.63 to -0.45; p-value < .03), and interim case fatality rates (*i*-CFR) data. To decisively arrive at dependable conclusions about the potential protective benefit gained from BCG vaccination in COVID-19, the ongoing or planned randomized controlled trials should consciously consider including measures of TI as: (a) all individuals immunized do not respond equally, (b) small study groups from higher background TI could fail to indicate any protective effect.

KEYWORDS

Bacillus-Calmette-Guérin (BCG), COVID-19, LTBI, SARS-CoV-2, trained immunity, tuberculin sensitivity test (TST)

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1 | BACKGROUND

There have been efforts to understand and explain the differential impact of COVID-19 on populations in pursuance of identifying protective variables that could predict the impact or be applied for intervention. Escobar et al.¹ and Berg et al.² had endeavored to explain/model the differential effect on populations based on 'trained immunity' correlates of countries as per Bacillus-Calmette-Guérin (BCG) vaccination rates after meticulous correction or fitting of the data for supposed major confounders like age, population density, development status, BCG coverage/implementation using the infections and mortality data from an early stage of pandemic (till April 22, 2020). However, other studies^{3,4} have failed to find support for the association previously observed between BCG vaccination policy or coverage and the impact of COVID-19 on populations when using updated data set. More recently, a study published by the Citizen science initiative of COVID-BCG Collaborative Working Group in Transboundary Emerging Diseases in April 2021 goes on to indicate BCG childhood vaccination as a risk factor for COVID-19.5 These conflicting assertions stem from fundamentally misplaced presumptions that BCG vaccination in childhood would provide lifelong protective or adverse effects completely disregarding the longevity of BCG vaccination conferred immunological correlates that seldomly last >5 years in the absence of revaccination, rechallenge, or exposure to environmental Mycobacterial spp.^{6–8}

The extrapolation of associative observations made previously^{1,2} linking BCG vaccination coverage to reduced COVID-19 impact on populations was expected to

disappear^{3,4,8} as the populations compared were at different phases of the wave-of-infections (WoI) so inherently inappropriate set for any correlative comparative analysis to indicate presumptive cause and effect association. Additionally, as the supposed 'trained immunity' conferred by childhood BCG vaccination usually wanes in <5 years.^{6,8} the BCG vaccination or coverage during childhood should not have any logical bearing on the COVID-19 outcomes in the most-impacted adult elderly population. Hence, the premise of protective 'trained immunity' from BCG vaccination given in childhood or to children in a population is not supposed to decrease the severity of infection or supposedly provide any protection in currently aged as the BCG conferred 'trained immunity' correlates would have waned away long ago.⁶⁻⁸ The use of early-stage pandemic data^{1,2} when the populations were not evenly exposed along with displayed associations' inherent disconnect with the mechanism proposed behind the observed protective correlation would make such assertions untenable. It was also highlighted by a study from Israel that found no significant association of the COVID-19 incidence among individuals, with regard to their childhood BCG vaccination status (vaccinated versus unvaccinated).9 The same may apply to studies that are using disparate data sets from a later stage of the COVID-19 pandemic and conclude the vaccinated countries to be more protected while overlooking the presence of countries with minimal COVID-19 effect in no BCG vaccination policy countries as well.¹⁰ Similarly, the studies trying to correlate childhood BCG vaccination to higher COVID-19 incidence or as a risk factor are also potentially indefensible due to gross overlooking of the basic facts about the longevity of trained

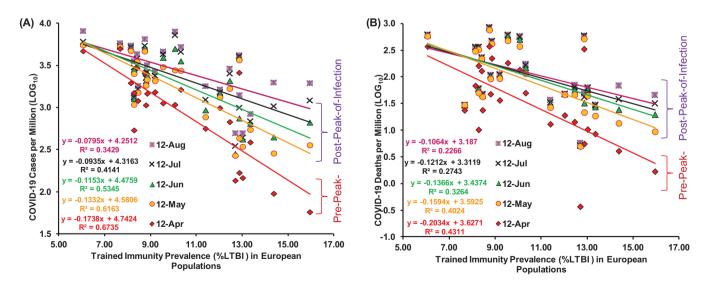


FIGURE 1 The COVID-19 cases (A) and deaths (B) in European countries with similar confounders and stages of pandemic consistently remained negatively and significantly correlated with trained immunity prevalence (est. %LTBI) starting from March 12 to August 26, 2020. Refer to Figure 2 for correlation analysis for the period starting from 12 March to 26 August 2020, covering the duration up to April 22 of Escobar et al.¹ and the August 1 reference point of Berg et al.² and beyond up to 1st February 2022.

TABLE 1		-UIV	19 dat	a (cast	es per	millic	on [Cr	iM] ai	COVID-19 data (cases per million [CpM] and deaths		r milli	on [D	pM]).	of Eur	opean	per million [DpM]) of European countries	ries											
Countries	CpM 12 Mar 2020	DpM 12 Mar 2020		CpM DpM CpM 26 Mar 26 Mar 12 Apr 2020 2020 2020		DpM 12 Apr 2020	CpM 1 26 Apr 2 2020	DpM 26 Apr 2020	CpM DpM 12 May 12 May 2020 2020	~	ay a	DpM CpM 26 May 12 Jun 2020 2020	M DpM un 12 Jun 0 2020	M CpM (un 26 Jun 0 2020	f DpM un 26 Jun) 2020	CpM n 12 Jul 2020	DpM 12 Jul 2020	CpM Dp 26 Jul 26 2020 203	DpM CpM 26 Jul 12 Aug 2020 2020	A DpM aug 12 Aug D 2020	CpM 5 26 Aug 2020	DpM 26 Aug 2020	CpM 31 Aug 2021	DpM 31 Aug 2021	CpM 1 Feb 2022	DpM 1 Feb 2022	Popula- LTBI tion 2017 (LTBI 2017 (%)
Spain	665.43	1.84	3118.24	93.35	4667.48 3	368.05	5243.71	495.96	5493.08 574.36		5622.58 595	595.47 5738.28	3.28 604.71	.71 5819.68	.68 606.06	6 6019.13	607.49	6584.73 608	608.11 8063.46	1.46 611.21	9581.54	619.60	103862.30	1804.25	214762.66	2003.05	46757733 6.06	
Iceland	342.51	0.00	2347.79	5.85	4979.54 2	23.42	5245.93 29.27		5272.28 29.27		5281.06 29.27	27 5289.84	9.84 29.27	1 5327.90	.90 29.27	5365.96	29.27	5406.94 29.27	.27 5772.87	.87 29.27	6094.88	29.27	29254.97	89.48	187577.28	124.73	341598 7.67	
Ireland	14.15	0.20	367.73	3.84	1950.46 6	67.52	3892.64	218.94	4697.25 300.01		4999.08 325.68	.68 5103.19	3.19 343.88	.88 5136.34	.34 348.93	3 5181.02	352.98	5232.17 356	356.21 5425.64	64 358.64	5733.94	359.24	70731.24	1021.89	238257.85	1231.41	4946514 8.14	
Finland*	19.67	0.00	172.86	0.90	536.62 1	10.10	825.68	34.28	1083.16 49.62		1195.93 56.30	30 1276.23	5.23 58.64	4 1297.52	52 59.18	1315.92	59.18	1333.97 59.36	.36 1378.89	60.09 68.	1443.85	60.45	23065.37	190.51	88875.62	358.66	5542120 8.28	
Netherlands*	35.82	0.29	433.52	25.32	1492.73 1	159.68	2207.86	261.07	2507.67 321.45		2659.00 341.64	.64 2827.19	7.19 353.13	13 2917.27	27 356.05	5 2976.60	357.91	3088.85 358	358.20 3536.95	.95 359.43	3973.74	362.58	113410.024	1051.70	268710.23	1244.51	17141028 8.29	
Switzerland*	100.18	0.81	1363.11	22.16	2933.15 127.64		3353.93 185.81		3506.16 215.47		3550.13 221.01	.01 3584.98	4.98 223.66	.66 3633.80	.80 226.43	3 3795.03	227.13	3971.49 228	228.17 4289.68	0.68 229.78	4690.84	231.17	89457.47	1250.53	258538.19	1459.81	8664751 8.42	
Norway*	147.38	0.18	621.22	2.58	1202.10 2	23.58	1386.69	37.03	1502.76 42.00		1544.40 43.29	29 1588.06	3.06 44.58	1627.11	11 45.87	1654.56	46.43	1679.62 46.98	.98 1802.32	.32 47.16	1935.15	48.64	29305.69	148.93	147153.42	263.47	5428015 8.46	
Belgium	34.40	0.34	537.60	41.30	2556.27	370.16	3977.84 (627.10 4	4637.01 753.16		4953.97 797.05	.05 5157.80	.80 821.97	97 5268.77	.77 829.30	0 5398.11	833.52	5667.21 836	836.63 6467.45	.45 843.18	7108.87	851.72	101842.33	2181.85	273737.07	2500.19	11597764 8.75	
Denmark*	116.30	0.00	323.87	7.07	1065.31 4	47.11	1479.60	72.82	1827.45 90.93		1971.87 97.14	14 2072.12	2.12 102.49	49 2187.04	.04 104.22	2 2233.80	105.08	2318.69 105	105.77 2600.29	0.29 107.15	2853.42	107.50	59465.86	444.50	307559.28	648.51	5795502 8.81	
France	44.04	0.93	446.50	25.97	1461.06 220.22		1907.82 349.69		2147.53 412.99		2229.12 436.54	5.4 2393.48	3.48 449.47	.47 2495.31	31 455.66	5 2635.48	3 459.23	2795.92 462	462.50 3165.48	.48 465.12	3883.60	467.77	100771.62	1698.01	290848.33	1948.61	65296963 8.86	
Germany*	32.75	0.07	524.15	3.19	1525.21 3	36.05	1882.08	71.29	2065.81 92.31		2162.64 101.38	.38 2233.77	3.77 105.73	73 2319.04	.04 107.67	7 2385.26	108.96	2466.27 109	109.79 2634.58	10.66	2851.10	111.56	46994.44	1098.92	118928.37	1406.12	83827321 9.20	
UK	7.89	0.13	155.54	12.92	1123.82 1	180.71	2038.02	352.76	3019.69 472.95		3536.57 532.41	.41 3906.24	6.24 577.36	36 4125.05	.05 592.38	8 4274.81	601.16	4406.99 605	605.08 4618.52	:52 608.29	4840.00	610.29	99698.56	1944.52	256137.43	2301.89	67943420 9.55	
Sweden*	76.27	01.0	296.36	13.26	1079.30 134.03		1865.89	253.13	2775.15 369.85		3523.17 438.21	3.21 4982.21	2.21 500.53	.53 6450.65	.65 536.53	3 7209.05	5 558.89	7504.02 568	568.68 7961.82	.82 573.53	8291.71	575.31	110905.06	1446.04	214948.41	1570.94	10109375 10.07	2
Portugal*	7.65	0.00	347.73	5.89	1627.29 4	49.45	2324.22	88.60	2738.77 114.11		3042.34 131.67	.67 3549.91	9.91 147.67	67 4009.69	9.69 152.57	4563.66	5 162.88	4921.99 168	168.47 5223.11	.11 173.08	5521.49	177.30	102078.57	1745.00	264625.33	1963.82	10191814 10.33	3
Czechia	10.92	0.00	189.32	0.84	561.32 1	12.88	693.23	20.54	769.50 26.42		846.98 29.59	59 929.87	87 30.71	71 1032.56	56 32.39	1231.77	32.86	1432.48 34.63	.63 1780.68	.68 36.50	2142.51	39.02	156574.27	2834.99	283749.26	3472.69	10712210 11.41	1
Estonia	20.35	0.00	405.52	0.75	986.67	18.84	1238.43	36.93	1316.07 45.98		1382.40 47.49	49 1484.91	4.91 47.49	1496.97	.97 47.49	1518.08	47.49	1533.15 47.49	.49 1638.68	.68 47.49	1741.94	48.24	107121.41	974.96	259631.09	1537.14	1326680 12.03	3
Turkey	0.01	0.00	42.96	0.89	674.17 1	14.18	1303.58	33.20	1674.60 46.09		1879.22 52.05	05 2074.01	4.01 56.56	6 2302.37	:37 59.95	2521.14	63.48	2676.28 66.44	.44 2892.80	.80 69.73	3107.22	73.19	75119.07	666.84	137842.26	1030.26	84482851 12.46	6
Slovakia	3.85	0.00	41.39	0.00	135.90 (0.37	252.56	3.30	268.31 4.94		277.10 5.13	3 282.41	41 5.13	300.91	91 5.13	348.16	5.13	399.08 5.13	3 492.67	67 5.68	647.61	6.04	143095.68	2302.69	292332.92	3275.67	5460073 12.70	0
Italy*	250.17	16.87	1333.08	136.33	2586.60 3	330.19	3269.98 441.89		3659.54 512.71		3814.12 546.69	.69 3909.39	9.39 567.70	70 3970.11	.11 576.73	3 4021.39	580.80	4071.91 583	583.34 4164.18	.18 585.29	4343.26	586.59	75205.92	2140.57	184145.90	2433.84	60447245 12.87	7
Poland*	0.819	0	77.72	0.37	167.94	5.49	297.86	13.84	431.37 21.42	42 571.54	.54 26.60	60 745.13	13 32.10	0 875.08	37.30	65.166	41.43	1126.18 43.97	.97 1399.36	.36 48.12	1666.54	52.24	76425.91	1993.41	130308.49	2789.48	37850425 12.88	8
Hungary*	1.66	0.00	27.03	1.04	146.02 1	10.25	258.90	28.17	343.09 44.01		390.52 51.68	8 419.73	73 57.48	8 427.39	39 59.86	438.47	61.62	459.28 61.72	.72 493.77	77 62.65	547.62	63.59	84318.39	3119.94	162217.22	4304.58	9656316 13.03	3
Lithuania*	1.10	0.00	100.65	1.47	386.81 8	8.449	523.82	15.061	545.50 18.36		600.59 23.14	14 643.57	57 27.18	8 663.41	41 28.65	685.09	29.02	735.05 29.39	.39 838.63	63 29.75	989.61	31.22	111 093.06	1695.63	256029.86	2936.21	2725537 13.36	6
Bulgaria*	1.007	0.144	34.83	0.43	95.13 4	4.03	179.465	7.915	286.40 13.384		350.15 18.709	709 444.13	13 24.18	8 634.39	39 30.367	7 1032.61	37.71	1484.078 48.64	.64 1974.83	.83 67.79	2243.52	82.32	66081.60	2739.88	139648.57	4843.65	6953085 14.38	8
Ukraine*	0.00	0.00	2.584	0.09	57.42 1	1.669	185.783	4.596	357.80 9.329	29 485.78	5.78 14.245	245 664.70	.70 19.53	3 914.81	31 24.398	8 1208.29	31.37	1461.78 36.36	.36 1933.24	.24 45.05	2517.17	53.00	54859.41	1311.44	98629.64	2463.63	43757273 15.95	5
Average (for countries < 10% LTBI)	130.04 1 0 %	040	867.68	20.37	2124.48 1	136.19	2786.82	228.00	3146.65 279.55		3308.86 298	298.10 3430.93	0.93 309.58	.58 3512.90	.90 313.42	2 3602.97	7 315.70	3746.07 317	317.17 4146.34	34 319.16	4582.58	321.65	72321.66	1077.09	220923.81	1290.91	8.37	
STDEV	192.73	0.55	938.59	26.17	1420.07 128.68	128.68	1509.03 196.92		1539.49 236.51		1572.01 251.32	.32 1583.06	06 260.70	.70 1588.63	.63 263.46	6 1619.76	265.23	1713.63 266	266.23 2009.51	9.51 267.91	2311.44 270.34	270.34	33503.91	735.13	70617.44	807.30 -	0.88	
Total Population of Comprise with	n of																										323282729	

12.62	1.61	283672884
2718.49	1137.86	
202009.08 2	58026.46 1	
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96906.53	30842.19	
149.01	205.97	
2813.35	2261.31	
2566.15 145.39	2215.65 206.71	
141.19	206.93	
2317.11	2148.41	
137.72	2091.14 205.55	
2147.42		
9 132.62	5 201.58	
1923.19	1916.26	
1677.50 126.35	1600.43 194.35	
1677.5		
33 115.43	5 180.57	
2 1430.33	4 1317.75	
84 102.22	71 163.84	
1263.84	0 1184.	
1032.81 78.93	1002.28 133.70 1184.71	
5 1032.	1 1002.	
708.71 49.15	70 96.01	
	9 765.70	
43 13.45	47 38.89	
237.43	372.47	
5 1.43	72.22 4.87	
- 31.1 > 10%	72.2	ttion es LTBI
Average (for 31.15 1.43 countries > 10% LTBI)	STDEV	Total Population of Countries with >10% LTBI

Note: * Countries are from Escobar et al. 2020¹
CpM: Cases per million; DpM: Deaths per million; Feb; February; Mar: March; Apr: April; Jun: June; Jul: July; Aug: August, Years as indicated.
LTRI estimates from Global Burden of Disease Collaborative Network; Global Burden of Disease Study 207 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (HME)¹⁸
LTRI estimates from Global Burden of Disease Collaborative Network; Global Burden of Disease Study 207 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (HME)¹⁸
LTBI estimates from Global Burden of Disease Collaborative Network; Global Burden of Disease Study 207 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (HME)¹⁸
LTBI estimates from Global Burden of Disease Collaborative Network; Global Burden of Disease Study 207 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (HME)¹⁸
STDEX: Standard deviation

0.1703

0.1326

1.7606

Adj. R²

Std. Err

0.3050

0.2734

1.0551

0.4311

0.4052

0.6009

0.4489

0.4238

0.5056

0.4024

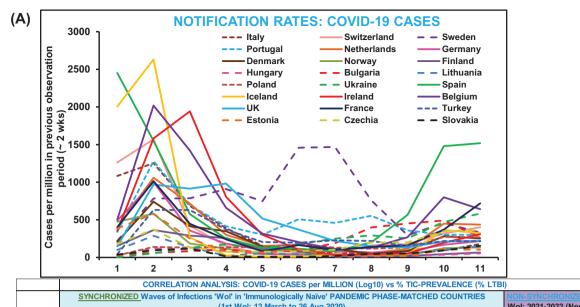
0.3752

0.499

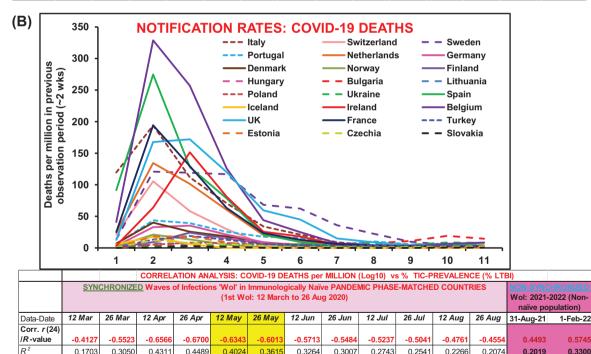
0.361

0.332

0.500



	SYNC	HRONIZEI	D Waves o	of Infection	s 'Wol' in '	Immunolog	gically Naïv	e' PANDE	MIC PHASI	E-MATCHE	D COUNT	RIES		RONIZED
					(1st Wo	ol: 12 Marc	h to 26 Au	g 2020)					Wol: 2021-2	022 (Non-
													naïve pop	ulation)
Data-Date	12 Mar	26 Mar	12 Apr	26 Apr	12 May	26 May	12 Jun	26 Jun	12 Jul	26 Jul	12 Aug	26 Aug	31-Aug-21	1-Feb-22
Corr. r (24)														
/R-value	-0.7572	-0.8066	-0.8207	-0.8062	-0.7851	-0.7642	-0.7311	-0.6891	-0.6435	-0.6107	-0.5856	-0.5711	0.2102	-0.2933
R ²	0.5733	0.6507	0.6735	0.6499	0.6163	0.5840	0.5345	0.4749	0.4141	0.3729	0.3429	0.3261	0.0442	0.0860
Adj. R ²	0.5540	0.6348	0.6587	0.6340	0.5989	0.5650	0.5133	0.4511	0.3875	0.3444	0.3130	0.2955	0.0007	0.0445
Std. Err.	0.9931	0.4309	0.3112	0.2789	0.2703	0.2700	0.2767	0.2841	0.2860	0.2855	0.2831	0.2760	0.2144	0.1579
F-value	29.5642	40.9771	45.3808	40.8368	35.3386	30.8784	25.2568	19.8988	15.5494	13.0824	11.4790	10.6469	1.0169	2.0710
p-value	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0007	0.0015	0.0026	0.0036	0.3242	0.1642



r	value	4.5153	9.6559	16.6689	17.9169	14.8131	12.4572	10.6610	9.4613	8.3139	7.4942	6.4473	5.7564	5.5639	10.8371	
F	o-value	0.0451	0.0051	0.0005	0.0003	0.0009	0.0019	0.0035	0.0055	0.0086	0.0120	0.0187	0.0253	0.0276	0.0033	
FIGURE	2 The	correla	tion be	etween	underl	ying pr	evailin	g traine	d imm	unity c	orrelate	s (%LT	BI) of I	Europear	populations	5
with COVII	D-19 case	es per n	nillion	(A) and	deaths	s per m	illion (I	B) and i	ts depe	endence	e on the	phase	of the p	andemio	. The observe	d
correlation (see botto	m corre	lation a	nalysis t	able) co	nsistent	tly remai	ined neg	ative fo	r the pe	riod. Th	e notific	ation ra	ites for co	untries	
with >10% L	TBI is in	dicated	by broke	en lines.	The co	rrelatior	n remain	ed high	with th	e synch	ronicity	of first p	eak of i	infections	(see	

0.3264

0.2958

0.5044

0.3007

0.2689

0.5051

0.2743

0.2413

0.5071

0.2541

0.2202

0.5078

0.2266

0.1915

0.5056

0.2074

0.1714

0.5034

0.2019

0.1656

0.3732

0.574

0.3300

0.2996

0.3211

immunity conferred from BCG vaccination and associated cross-reaction.⁵ The conclusions drawn by the recent report of the Citizen science initiative of COVID-BCG Collaborative Working Group may call for more conservativism and greater scrutiny due to the comparison of groups that have disproportionate representation of individuals from disparate underlying *Mycobacterium spp*. conferred background trained immunity as suggested by us previously.⁶

We reason, the dependability on the correlative associations as well as conclusions presented in previous studies^{1,2-5} would have tremendously improved on considerations: (a) direct measure of prevailing supposed protective 'trained immunity' correlate (TIC) as a result of populations exposure to Mycobacterium spp. or BCG vaccination,⁶⁻⁸ that is, Tuberculin positivity [TIC of BCG given at birth wanes within <5 years,⁷ so chances of supposed heterologous protection^{5,10,11} of elderly from childhood vaccination are remote]; (b) analysis of countries at a similar stage of the pandemic; (c) underlying confounders including potential contributory variables (e.g., Vitamin D, Zinc)¹²⁻¹⁴; (d) the correlations observed, at any time, to be the total sum of the effects from protective variable and preventive or curative measures in place (e.g., social distancing norms and adherence, medical infrastructure/support) and trained immunity being acquired as a result of natural infection or vaccination.

The European populations with quite dissimilar BCG coverage (including no vaccination)¹⁵ that have had almost simultaneous *WoI* during the pandemic but experienced differential COVID-19 impact¹⁶ offer an excellent opportunity to evaluate the alternative hypothesis that if BCGs could be of any protective benefit the 'trained immunity from *Mycobacterium* spp. exposure (BCG or environmental NOT necessarily the childhood vaccination coverage *per se*) would display protective covariation (negatively covary) with COVID-19 incidence and mortality among socially similar countries as was suggested by us previously.⁶ It would be theoretically better equipped to

predict the outcome or potentially flattened curve if any such association exists, that may have a cause and effect relationship. The current analysis of TIC and COVID-19 data from 24 socially similar European countries, completely disregarding their vaccination coverage or policy, support a potential protective role for the prevalent TIC of populations on COVID-19 incidence and mortality.

2 | MATERIAL AND METHODS

The COVID-19 incidence and mortality data for the European countries (Table 1) for first WoI (March to Aug 2020) was obtained from Worldometer and that for August 2021 and February 2022 from https://ourworldindata.org/ covid-cases [compiled from JHU CSSE COVID-19 Data; Accessed on 28 March 2022] and that of East and West Germany states from https://www.citypopulation.de/en/ germany/covid/ [Accessed on 10 October 2020] and previously published estimates.^{6,8} The latent tuberculosis infection (LTBI)¹⁷ prevalence estimates for populations (i.e., 'TIC') were from Institute for Health Metrics and Evaluation.¹⁸ All statistical estimations and correlation analysis of the COVID-19 incidence and mortality with TIC or LTBI prevalence of populations (average, standard deviation (STDEV), standard error, F-value, correlation/Pearson coefficient (r/R), regression, etc.) were performed using Microsoft Excel 2019. The p-values <0.05 were considered significant unless explicitly stated otherwise. The methodology employed has been essentially the same as described previously.^{6,12,13}

3 | RESULTS & DISCUSSION

Analysis of the updated COVID-19 data (till 28 August 2020, Table 1,¹⁶ from 24 European countries with similar confounders (refer¹ and additional), stage of the pandemic and without any exclusions (applied in 1,4) consistently displayed protective or negative correlation with the direct

Note. The highlighted 12th May *and* 26th May values could reflect the assumed total sum of actual maximum achievable correlation for potential 'trained immunity' along with current confounders and the stringent measures put in place by the countries to reduce the spread of COVID-19—*Not* necessarily due to only the prevailing trained immunity of the populations as a result of BCG coverage or implementation alone as assumed.^{1,3} Even if there is a cause and effect relationship, the expected protective covariation (correlation) would expectedly further go down for the reasons mentioned above primarily due to increasingly heterogenous (loosened) response combined with changing trained immunity prevalence.

corresponding notification rates graph above for the data on date indicated in the table below) and been on decline since then partially resulting from the loss of synchronicity, populations response, acquired immunity, and understandably and importantly the changing reporting and management practices. *Refer to Supporting information* Figure S1 *from European CDC that more accurately reflects the waves of infections or deaths from starting not explicitly observable in the figure presented here due to the coarse methodology employed*. The response of populations had been more stringent and uniform for first wave of infections.

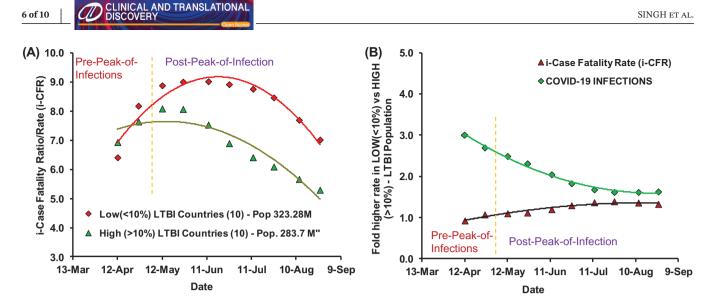


FIGURE 3 The COVID-19 cases, deaths, and CFR consistently remained lower in European populations with higher trained immunity (TI) correlate (>10% LTBI) post-peak-of-infections than in countries with the lower TI-correlate (<10% LTBI). The TI-correlate indicated a significant consistently negative association with COVID-19 infections (Pearson correlation r(24): -0.79 to -0.57, p-value < .005) and mortality [r(24) = -0.63 to -0.45, p-value < .05)] for the whole time period (12 March to 26 August 2020). Refer to Figure 1 in conjunction with Figure 2 for detailed correlation analysis and its variation with the wave of infections across 24 countries. Refer to Table 1 for updated COVID-19 cases and deaths data for the 24 countries with supposedly similar confounders and at a similar stage of pandemic included in the study. (A) The i-CFR [(deaths/cases)*100] for low LTBI countries had remained higher than that of high LTBI countries post infections peak. (B) Low LTBI countries have had relatively higher infections per million population (1.63-fold on 26 August 2020) and consistently higher i-CFR (\sim 30% on 26 August 2020).

measure of desired heterologous TIC of populations (i.e., tuberculin positivity without active tuberculosis disease; referred by WHO as LTBI for the management purposes only due to slight chance of reinfection and reactivation in a small minority of individuals (WHO,¹⁷ IHME¹⁸). Higher LTBI prevalence populations consistently displayed lower COVID-19 incidence and mortality per million (Table 1). The overall cases and mortality among European countries with similar confounders^{1,2,6} consistently remained negatively and significantly correlated with the prevalence of trained immunity correlate (%LTBI) for populations (Figure 1A & B). The correlative association displayed dependence on the phase of the pandemic (Figure 2A, B & Supporting information Figure S1). The countries with lower LTBI prevalence (<10%) reported higher incidence and fatalities during the study period (12 March 2020 to 26 August 2020) as compared to their higher LTBI prevalence (>10%) neighbors. Surprisingly, some outliers that had displayed lower deaths and infections despite lower TIC or higher infections and death despite relatively higher TIC prevalence are expectedly countries with higher Vitamin D and Zn sufficiency, respectively.^{12,13} The correlation between TI estimate (%LTBI) and cases and mortality for COVID-19 consistently remained negative post-peak-of-infections (cases per million: r(24): -0.79 to -0.57; *p*-value: < .004; mortality per million (*r*(24): -0.63) to -0.45; p-value: <0.03). The i-CFR among low (<10%)

LTBI prevalence countries remained much higher than that among high LTBI prevalence countries (Figure 3A). With the progression of the COVID-19 pandemic, the relative CFR between the groups of countries seem to be steadily increasing while incidence rates had been falling (Figure 3B). The correlations observed shown here are supposed to decline further before the disappearance of COVID-19 due to progressive loss of synchronicity of infections or pandemic phases (Figure 2A & B), lower prevalence of the protective variable (6.06–15.95%),¹⁸ the differential response of the study population, etc. not necessarily due to the supposed absence of correlation as proposed by Arlehamn et al.³ The apparent progressive closing of the gap in COVID-19 impact on differential TIC prevailing populations (<10 and >10% LTBI) would be also being contributed by interventions or measures undertaken, for example, the introduction of vaccines and development of a gradual increase in herd immunity, changing COVID-19 stringency measures (https://ourworldindata. org/grapher/covid-stringency-index accessed on March 28, 2022),¹⁹ confusions regarding fever management that controls pertinent immune responses (cell-mediated and antiviral),^{20,21} possible over prescription or self-medication of supposed immune augmenting agents like Vitamin D¹³ and Zinc.14,22,23

The East and the West Germany States that have been proposed in the early stage of the pandemic to be

1 A B L E 2 COVID-19 cases and deams of erstwhile East and west Germany states. https://www.citypopulauon.de/en/germany/covid/ [Accessed on 10 October 2020]	erstwinde Ea	ast and west	Germany s	tates. nups:/	/www.citypo	opulation.de	/en/german	y/covia/ [A	ccessed on I	U UCIODEL 21	โกรเ	
EAST GERMANY (Region)	COVID-1	COVID-19 Cases per	er 100k population	lation			COVID-1	9 Deaths p	COVID-19 Deaths per million population	population		
States、Dates	10-Apr	8-May	5-Jun	3-Jul	31-Jul	28-Aug	10-Apr	8-May	5-Jun	3-Jul	31-Jul	28-Aug
Berlin: City State	133.5	173.4	193.5	232.2	256.6	308.3	NA	44.42	54.5	58.32	60.23	60.77
Brandenburg	84.74	122.6	129.2	136.2	142	154.2	19.03	51.95	61.86	65.82	66.22	66.22
Mecklenburg-Vorpommern [Mecklenburg -Western Pomerania]	38.31	45.46	48.13	50	55.09	62.93	6.84	11.81	12.44	12.44	12.44	12.44
Sachsen [Saxony]	94.33	121.2	130.8	134.1	136.4	147.2	15.72	45.19	52.06	55.01	55.26	55.26
Sachsen-Anhalt [Saxony- Anhalt]	54.9	75.09	78.55	86.11	92.17	102.1	8.201	21.87	25.06	26.88	28.25	29.16
Thüringen [Thuringia]	73.55	122.3	<u>145</u>	<u>153.5</u>	158.6	169.7	11.25	52.5	79.22	84.84	85.31	85.31
Average (without Berlin)	65.27	91.01	100.62	105.93	110.57	120.48	10.50	32.84	42.20	44.79	45.32	45.54
Average (with Berlin)	79.89	110.01	120.86	132.02	140.14	157.41	12.21	37.96	47.52	50.55	51.29	51.53
WEST GERMANY (Region)	COVID-1	COVID-19 Cases per	er 100k population	ulation			COVID-1	9 Deaths p	COVID-19 Deaths per million population	population		
Bremen: City State	72.52	164.1	225.6	246.9	262.8	292	19.08	46.98	64.59	77.8	80.74	82.21
Hamburg: City State	218.2	269	275.7	281.8	294.5	340.6	28.69	108.8	137	140.7	140.7	141.3
Baden-Württemberg	235.7	301.5	315.5	323.2	337.6	378.5	55.31	136.5	160.2	165.7	165.7	166.4
Bayern [Bavaria]	264.7	340.3	361.5	371.7	389.7	437.2	54.93	161.1	189	197.9	199.3	199.8
Hessen [Hesse]	101.8	143.4	162.6	174.6	193.7	246.9	17.81	64.09	76.65	80.95	81.74	82.7
Niedersachsen [Lower Saxony]	102.8	136.7	156.7	171	182.1	209.8	21.39	61.67	75.56	79.19	80.56	81.44
Nordrhein-Westfalen [North Rhine-Westphalia]	150.1	195.8	215.7	245.8	275.7	327.8	27.97	77.84	90.1	93.94	95.34	96.56
Rheinland-Pfalz [Rhineland- Palatinate]	121.1	154.3	165.6	173	184.9	219.7	14.66	46.9	56.18	57.4	58.14	58.38
Saarland	209.2	263.4	272.9	277.6	285.7	309.7	NA	141.9	168.2	176.3	176.3	176.3
Schleswig-Holstein	76.76	101	<u>107</u>	110	<u>119.9</u>	<u>139.6</u>	NA	42.01	50.28	52.35	<u>53.03</u>	53.72
Average (without Bremen & Hamburg)	157.77	204.55	219.69	230.86	246.16	283.65	32.01	91.5	108.27	112.97	113.76	114.41
Average (with Bremen & Hamburg)	155.29	206.95	225.88	237.56	252.66	290.18	29.98	88.78	106.78	112.22	113.16	113.88



TABLE 3 I-CFR rates in East and West Germany region or states

EAST GERMANY (Region) i-CFR RATES AT INDICATED DATES

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Brandenburg-Vorpommern4.2374.7884.8334.6634.294[Mecklenburg-Western Pomerania]2.5982.5852.4882.2581.977Sachsen [Saxony]3.7293.9804.1024.0513.754Sachsen Saxony- Anhalt]2.9133.1903.1223.0652.856Thüringen [Thuringia]4.2935.4635.5275.3795.027Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.6094.1944.2294.0983.780Bremen: City State2.8633.9323.8293.6593.274Baden-Württemberg2.8632.8633.1513.0722.815Bagern [Bavaria]4.0454.9694.9934.7784.149Bagern [Bavaria]4.7345.2285.3245.1144.570Hessen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Sarland5.3876.1636.3516.1715.693Sarland5.3876.1636.3516.1715.693Sarland4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	States\Date	8-May	5-Jun	3-Jul	31-Jul	28-Aug
[Mecklenburg-Western Port and Sachsen [Saxony]2.5982.5852.4882.2581.977Sachsen [Saxony]3.7293.9804.1024.0513.754Sachsen-Anhalt [Saxony-Anhalt]2.9133.1903.1223.0652.856Thüringen [Thuringia]4.2935.4635.5275.3795.027Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.4503.9323.8293.6593.274WEST GERMANY (Region)3.0722.815Hamburg: City State2.8632.8633.1513.0722.815Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland-Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Berlin: City State	2.562	2.817	2.512	2.347	1.971
Sachsen [Saxony]3.7293.9804.1024.0513.754Sachsen-Anhalt [Saxony-Anhalt]2.9133.1903.1223.0652.856Thüringen [Thuringia]4.2935.4635.5275.3795.027Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.6094.1944.2294.0983.780Kest GERMANY (Region)5.8633.8203.8293.6523.274Bremer: City State2.8632.8633.1513.0722.815Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Nicdersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen[North Rhine-Westphalia]3.974.1773.8223.4582.946Sarland5.3876.1636.3516.1715.693Sarland5.8876.1636.3516.1715.693Schleswig-Holstein4.5994.6994.7594.4233.848Average (without Bremen & Hamburg)4.734.9284.8934.6214.034	Brandenburg Mecklenburg-Vorpommern	4.237	4.788	4.833	4.663	4.294
Sachsen-Anhalt [Saxony- Anhalt]2.9133.1903.1223.0652.856Thüringen [Thuringia]4.2935.4635.5275.3795.027Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.4503.9323.8293.6593.274WEST GERMANY (Region)	[Mecklenburg-Western Pomerania]	2.598	2.585	2.488	2.258	1.977
Thüringen [Thuringia]4.2935.4635.5275.3795.027Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.4503.9323.8293.6593.274WEST GERMANY (Region)	Sachsen [Saxony]	3.729	3.980	4.102	4.051	3.754
Average (w/o Berlin)3.6094.1944.2294.0983.780Average (with Berlin)3.4503.9323.8293.6593.274Average (with Berlin)3.4503.9323.8293.6593.274WEST GERMANY (Region)	Sachsen-Anhalt [Saxony- Anhalt]	2.913	3.190	3.122	3.065	2.856
Average (with Berlin)3.4503.9323.8293.6593.274Average (with Berlin)3.4503.9323.8293.6593.274WEST GERMANY (Region)2.8632.8633.1513.0722.815Bremen: City State2.8632.8633.1513.0722.815Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Thüringen [Thuringia]	4.293	5.463	5.527	5.379	5.027
WEST GERMANY (Region)Bremen: City State2.8632.8633.1513.0722.815Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Average (w/o Berlin)	3.609	4.194	4.229	4.098	3.780
Bremen: City State2.8632.8633.1513.0722.815Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Average (with Berlin)	3.450	3.932	3.829	3.659	3.274
Hamburg: City State4.0454.9694.9934.7784.149Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	WEST GERMANY (Region)					
Baden-Württemberg4.5275.0785.1274.9084.396Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Bremen: City State	2.863	2.863	3.151	3.072	2.815
Bayern [Bavaria]4.7345.2285.3245.1144.570Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Hamburg: City State	4.045	4.969	4.993	4.778	4.149
Hessen [Hesse]4.4694.7144.6364.2203.350Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Baden-Württemberg	4.527	5.078	5.127	4.908	4.396
Niedersachsen [Lower Saxony]4.5114.8224.6314.4243.882Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Bayern [Bavaria]	4.734	5.228	5.324	5.114	4.570
Nordrhein-Westfalen [North Rhine-Westphalia]3.9754.1773.8223.4582.946Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Hessen [Hesse]	4.469	4.714	4.636	4.220	3.350
Rheinland-Pfalz [Rhineland- Palatinate]3.0403.3933.3183.1442.657Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Niedersachsen [Lower Saxony]	4.511	4.822	4.631	4.424	3.882
Saarland5.3876.1636.3516.1715.693Schleswig-Holstein4.1594.6994.7594.4233.848Average (without Bremen & Hamburg)4.4734.9284.8934.6214.034	Nordrhein-Westfalen [North Rhine-Westphalia]	3.975	4.177	3.822	3.458	2.946
Schleswig-Holstein 4.159 4.699 4.759 4.423 3.848 Average (without Bremen & Hamburg) 4.473 4.928 4.893 4.621 4.034	Rheinland-Pfalz [Rhineland- Palatinate]	3.040	3.393	3.318	3.144	2.657
Average (without Bremen & Hamburg) 4.473 4.928 4.893 4.621 4.034	Saarland	5.387	6.163	6.351	6.171	5.693
	Schleswig-Holstein	4.159	4.699	4.759	4.423	3.848
Average (with Bremen & Hamburg) 4.290 4.727 4.724 4.479 3.924	Average (without Bremen & Hamburg)	4.473	4.928	4.893	4.621	4.034
	Average (with Bremen & Hamburg)	4.290	4.727	4.724	4.479	3.924

Note. East Germany states (estimated LTBI 22.5%⁹, consistently reported lower i-CFR as compared to the West Germany States (estimated LTBI 9.2% LTBI.⁷ Eastern Germany with higher trained immunity correlates consistently had 20–30% lower CFR as compared to Western Germany states. The inclusion of Berlin in the East Germany region, and of Hamburg and Bermen in the West Germany region decreased the closing trend of the i-CFR with the passage of time (compare covariation of red and green trend lines with orange and light green in Figure 4C) that could be reflective of more LTBI positives in Berlin as compared to Hamburg and Bremen.

experiencing differential COVID-19 impact^{1,3} due to differential BCG coverage and policy provide a unique opportunity to test our assertion that actual trained immunity correlates (%LTBI) to be responsible for differential COVID-19 impact. The estimated TIC (%LTBI prevalence) of East and the West Germany States are 22.5 and 9.2%, respectively.⁷ The East Germany States with higher TIC have experienced two-fold cases while more than two-fold fewer deaths from COVID-19 per million populations during the study period (Table 2; data from https://www.citypopulation.de/en/germany/covid/). The inclusion or exclusion of city states did not change the supposed overall protective effect on populations. Similarly, the CFR for East and West Germany states remained significantly different for the whole period (Table 3). The COVID-19 incidence and death rates remained significantly different between East and West Germany States (Figure 4A & B) both pre- and postpeak-of-infections consistent with the potential protective role of TIC prevalence in populations. The CFR rates also remained consistently different during the study period (from 10th April to 28 August 2020; Figure 4C)

without requiring any correction factors. However, the differential response gap seen for East and West Germany States is showing signs of closing as expected for populations slowly reaching toward stable equilibrium with underlying confounders (Figure 4C).

4 | CONCLUSIONS

In conclusion, we believe the incidences, mortality, and i-CFR of COVID-19 would negatively correlate with the trained immunity of populations that have comparable underlying confounders, not the BCG coverage *per se* till the populations remained naïve to SARS-CoV-2 infections and populations responded more equally. To decisively arrive at dependable conclusions about the potential protective benefit of BCG in COVID-19, the ongoing or planned randomized 28 controlled trials (Supporting information Figure S2, Supplementary Tables 1–4) should consciously consider including measures of TIC^{10,24} as— (a) all individuals immunized do not respond equally (up to 10–15% could be non-responders), (b) small study

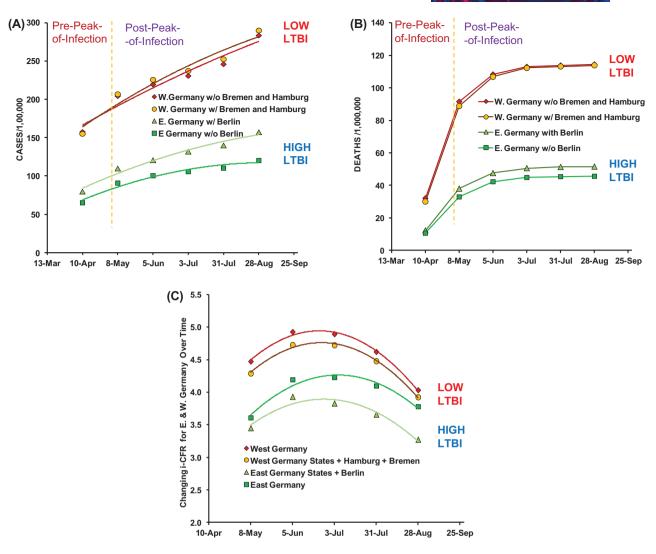


FIGURE 4 East Germany (E. Germany) states with higher trained immunity correlate (%LTBI) as compared to West Germany (W. Germany) states (22.5 vs. 9.2%) consistently reported lower COVID-19 cases (A), Deaths (B), and i-CFR (C) during the study period (10th April to 28th August). Refer to Table 2 for COVID-19 cases and deaths and Table 3 for i-CFR estimates. The E. Germany states consistently had 20–30% lower i-CFR as compared to W. Germany states. The inclusion of Berlin in the East Germany region, and of Hamburg and Bremen in the West Germany region decreased the closing trend of the i-CFR with the passage of time (compare covariation of red and green trend lines with orange and light green in [C], possibly indicative of more LTBI positives in Berlin than in Hamburg and Bremen. In the future, as the pandemic progresses, the gap between E. and W. Germany states is expected to close, partially resulting from a decrease in the vulnerable population and the concomitant increase in the population's overall 'trained immunity' as a result of infections and inoculations (asymptomatic or symptomatic; BCG or others, including SARS-CoV-2).

groups of higher background trained immunity could fail to indicate any protective effect. Additionally, the inclusion of individuals who might have been exposed previously/recently to SARS-CoV-2 (asymptomatic or symptomatic) would tend to skew the trial outcomes toward displaying non-protection. In concurrence with our assertions, the TST positivity has been recently observed to be associated with three times lower SARS-CoV-2 infections and protection from severe COVID-19.²⁵ Currently, under development COVID-19 vaccines still have a long way to go and be available in sufficient supply to cover the whole global population at the same time to confer the much-needed and touted 'herd immunity' whereas BCG is readily available which can be scaled up at a lower cost to provide the needed respite to vulnerable populations, especially in poor countries. Any potential protective effect displayed by BCG vaccination in the ongoing trials, especially in the aged and persons with comorbidities who are currently accounting for more than 90% of deaths, could help to provide hope in the current scenario. Nevertheless, study design improvements remain desired for increasing our confidence in the outcomes of the ongoing clinical trials evaluating the potency of BCG for COVID-19 control.

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CONFLICT OF INTEREST

The authors declare no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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