

1 **Regional BCG vaccination policy in former East- and West-Germany may impact on**
2 **both severity of SARS-CoV-2 and incidence of childhood leukemia.**

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23 We read with great interest the recent thorough study from Miller et al. [1], who reported a
24 beneficial impact of early Bacillus Calmette–Guérin (BCG) vaccination and linked morbidity
25 and mortality due to SARS-CoV-2 with BCG vaccination policy. They found that countries
26 without policies of universal BCG vaccination (like Italy, the Netherlands or the USA) have
27 been more severely affected compared to countries with universal and long-standing BCG
28 policies. Since senior citizens are particularly sensitive to COVID-19, newborn vaccination
29 programs implemented in the 1940s and 1950s should be the most beneficial. Thus, we were
30 impressed by the linear correlation between the year of the establishment of universal BCG
31 vaccination and the mortality rate presented by Miller et al. [1]. In our view, this is a
32 convincing argument for the hypothesis that the earlier the vaccination policy was
33 established, the larger the segment of the elderly population being protected.

34 We would like to make the scientific community aware of a unique historical circumstance in
35 Germany, where divergent BCG vaccination policies existed in the politically divided country
36 (1949-1989) before German reunification in 1990. In East Germany, BCG vaccination
37 programs were established by the communist government in 1951 and soon became
38 compulsory in 1953, leading to near-universal (99.8%) BCG vaccination of newborns by day
39 3. By contrast, voluntary BCG vaccination (recommended since 1955) was far less common
40 in West Germany, due to low incidence of the disease after the Second World War. In early
41 years, only 7-20% of all newborns became BCG-vaccinated in Western Germany, with
42 almost complete cessation of vaccination between 1975 and 1977 (**Figure 1A**). Thus, we
43 believe that the comparison of morbidity and mortality of SARS-CoV-2 would be particular
44 informative in the light of the rather uniform genetic, social and cultural background. Here, we
45 record those data in formerly East and West German federal states (excluding Berlin, **Figure**
46 **1B**). Our observations strongly support the analysis from Miller et al., and point towards BCG
47 vaccination having a protective effect. We did not observe a significant difference in the
48 lethality of SARS-CoV-2; once people became infected, the course of disease is not
49 significantly different between formerly East and West German parts of the reunified country.

50 It is fair to conclude that, 30 years after German reunification, the standard of intensive care
51 has been completely harmonized throughout the country and at the time of our analysis the
52 health care system in Germany still had large capacities. Besides BCG vaccination, we
53 cannot exclude other factors influencing morbidity and mortality, e.g. the speed of the
54 pandemic spread, differences in the social behavior, or the potentially greater likelihood of
55 being infected with SARS-CoV-2 in the larger cities of Western Germany. We also
56 acknowledge the fact that statistical correlation does not prove causation but SARS-CoV-2
57 testing capacities, a frequent confounding factor when comparing different populations
58 across countries, were early on expanded to far more than 100 000/day (end of March 2020)
59 all over Germany. Furthermore, demographic characteristics show that relatively more
60 elderly people live in East Germany than in West Germany. The age distribution shows that
61 the proportion of people above 64 years of age is generally higher in Eastern federal states
62 formerly belonging to the German Democratic Republic (GDR) [2]. Thus, age-wise, the
63 population with a greater risk to succumb due to COVID-19 is even more abundant in East,
64 compared to West Germany.

65 We would like to remind readers that a correlation between BCG vaccination and reduced
66 disease risk beyond tuberculosis has long been suspected. In particular, many older studies
67 link BCG vaccination to a lower cancer risk, and there was even an international symposium
68 held in 1982 entitled “BCG Vaccination against Cancer and Leukemia” (Chicago). Mortality
69 related to childhood leukemia was reported to be significantly reduced in a retrospective
70 study of 54 414 BCG-vaccinated vs. 172 986 non-vaccinated infants in Chicago [3]. The
71 question was brought up again in 1978 in a meta-analysis of Rosenthal's data, and two other
72 cohorts confirmed the initial observation [4]. With respect to childhood leukemia, the
73 potentially beneficial effects of the East German BCG vaccination program were also
74 reported by Spix et al. [5]. The authors compared the rate of childhood leukemia before and
75 after German reunification. Somewhat counterintuitively, the rate of childhood leukemia was
76 clearly lower in the former GDR (East Germany) with 3/100 000 children compared to

77 3.7/100 000 in former West Germany, but reached West German levels approximately 8
78 years after reunification with then 4 cases of acute lymphoblastic leukemia (ALL)/100 000
79 children below 15 years of age. It should be emphasized that cancer registries were
80 exemplary in the former GDR, and thus this “catch-up effect” cannot be attributed to poor
81 registration. In addition, meta-analysis of several epidemiological studies has shown that
82 protection from childhood ALL, the most common malignancy in children, is observed only
83 when children are vaccinated with BCG very early in life (< than 3 months) [6].

84 In recent years, a new immunological concept – trained immunity – has emerged, improving
85 our understanding of the role of BCG vaccination in shaping the innate immune memory
86 response. Innate immune cells, such as macrophages, monocytes or NK cells, can change
87 their epigenome after exposure to infection, vaccination or other stressors, which modifies
88 their expression profile and cell physiology [7]. BCG vaccination in particular, educates
89 hematopoietic stem cells and generates trained monocytes and macrophages [8]. In a
90 double-blinded, placebo controlled study with healthy male subjects who were challenged by
91 attenuated Yellow Fever Virus after having received a BCG-vaccine or placebo, the viremia
92 was significantly lower in the vaccinated group [9]. Besides infection with SARS-CoV-2 and
93 childhood ALL, there may be many other malignant and non-malignant, e.g. infectious
94 diseases for which measures that augment our innate immune responses are beneficial [10,
95 11]. However, it remains unclear to date whether BCG vaccination across different age
96 groups, e.g. newborns, adolescents, young and elderly people, has uniformly the same
97 beneficial effect.

98 With regard to the current SARS-CoV-2 pandemic situation, we fully support the idea of
99 implementing controlled clinical trials for BCG vaccination, as already started by Curtis et al.
100 [12]. Only well-controlled clinical trials may prove a benefit of this old vaccine that was
101 developed by the two French immunologists almost 100 years ago. Low-and medium income
102 regions like Africa or India may benefit mostly if such trials proof a clinical benefit, at least
103 until a specific and effective SARS-Cov-2 vaccine becomes available.

104 **Author contributions**

105 JH, designed research, analyzed data and wrote the paper. UF, wrote the paper. FA,
106 analyzed data, performed research and wrote the paper. AB, designed research, analyzed
107 data and wrote the paper.

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109 **Conflict-of-interest disclosure**

110 The authors declare no conflict of interests.

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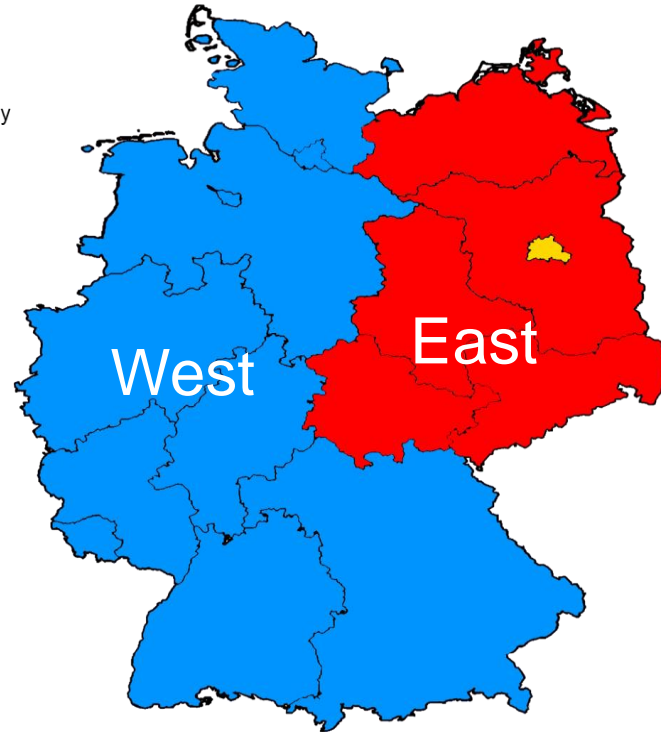
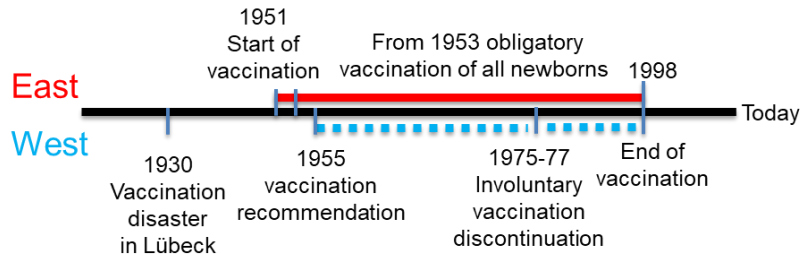
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151 **Figure legend:**

152 **Fig 1: Morbidity and mortality due to SARS-CoV-2. (A)** Vaccination policy in East and
153 West Germany. When BCG vaccination was first introduced against tuberculosis in Germany
154 (in the city of Lübeck) in 1930, tragically 131 newborns fell ill and 77 died due to a
155 contamination of the vaccine with virulent tubercle bacilli. This was the greatest vaccination
156 disaster of the 20th century and delayed introduction of BCG vaccination in Germany till after
157 World War II. **(B)** Morbidity and mortality due to SARS-CoV-2 in federal states formerly
158 belonging to East and West Germany, excluding Berlin. Data were extracted from Johns
159 Hopkins University (as per 28.4.2020). Population numbers were extracted for the federal
160 states as per Dec.2018 (www.statista.com).

A



B

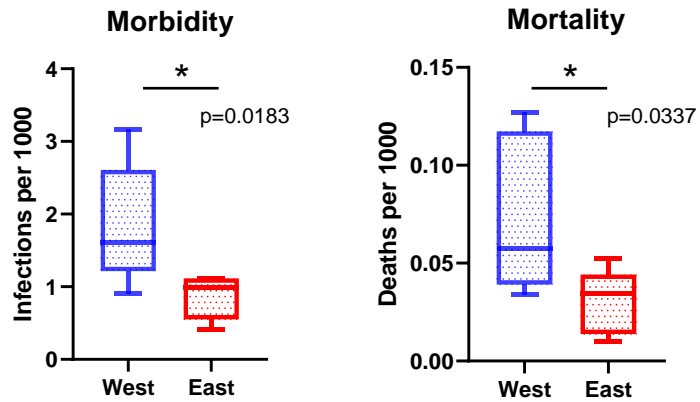


Figure 1: Hauer et al.