Journal of Alzheimer's Disease 98 (2024) 361–372
DOI 10.3233/JAD-231323
IOS Press

Review

Vaccines and Dementia: Part II. Efficacy of BCG and Other Vaccines Against Dementia

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Accepted 15 January 2024
Pre-press 19 February 2024

Abstract. There is growing awareness that infections may contribute to the development of senile dementia including Alzheimer's disease (AD), and that immunopotentiation is therefore a legitimate target in the management of diseases of the elderly including AD. In Part I of this work, we provided a historical and molecular background to how vaccines, adjuvants, and their component molecules can elicit broad-spectrum protective effects against diverse agents, culminating in the development of the tuberculosis vaccine strain Bacille Calmette–Guérin (BCG) as a treatment for some types of cancer as well as a prophylactic against infections of the elderly such as pneumonia. In Part II, we critically review studies that BCG and other vaccines may offer a measure of protection against dementia development. Five studies to date have determined that intravesicular BCG administration, the standard of care for bladder cancer, is followed by a mean ∼45% reduction in subsequent AD development in these patients. Although this could potentially be ascribed to confounding factors, the finding that other routine vaccines such as against shingles (herpes zoster virus) and influenza (influenza A virus), among others, also offer a degree of protection against AD (mean 29% over multiple studies) underlines the plausibility that the protective effects are real. We highlight clinical trials that are planned or underway and discuss whether BCG could be replaced by key components of the mycobacterial cell wall such as muramyl dipeptide. We conclude that BCG and similar agents merit far wider consideration as prophylactic agents against dementia.

Keywords: Alzheimer's disease, Bacille Calmette–Guérin, dementia, herpes zoster, immunopotentiation, influenza, muramyl dipeptide, trained immunity, vaccine

DEMENTIA AND INFECTION

Pulmonary diseases caused by influenza virus, pneumococcus, adenoviruses, and other infectious agents are a major cause of death in the very elderly, and broad-spectrum immune boosting ('trained immunity') with Bacille Calmette–Guérin (BCG) has been shown to offer significant protection against respiratory infections in the elderly [1]. The increased prevalence of infectious diseases in the elderly (and perhaps the aging phenotype itself) has been argued to culminate from age-related decline in stem cell renewal that most centrally affects the immune system [2]. Indeed, there is growing interest in the potential involvement of microbes in the pathoetiology of dementias including Alzheimer's disease (AD) as well as in Parkinson's disease, and perhaps also some cancers and diseases of the heart and vasculature.

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Key observations are that the signature protein of AD brain, amyloid-β (Aβ) peptide, has a conserved physiological role as part of the immune system. Acting as an antimicrobial peptide (AMP), Aβ forms extracellular traps that entrap and inactivate pathogens and protect host cells from infection [3–5], prompting the antimicrobial protection hypothesis of AD [6]. Furthermore, brain tissue of AD patients displays extensive signatures of infection/inflammation including macrophage infiltration and cytokine upregulation/neuroinflammation [7–9] as well as Aβ deposition. The product of the key *APOE* gene, whose different alleles (ε2, ε3, and ε4, referred to as *APOE2–APOE4*) modulate AD risk, binds tightly to Aβ [10] and APOE-derived peptides themselves have direct antimicrobial activity (e.g., [11–13] and references therein). Moreover, *APOE* modulates the risk of diverse infectious diseases (reviewed in [14]): *APOE4* accelerates HIV proliferation whereas *APOE3* is protective [15], there was a higher bacterial load in *Chlamydia*-infected homozygous *APOE4* patients than in *APOE2*/*APOE3* carriers [16], and *APOE4* increases susceptibility to herpes simplex lesions [17]. *APOE4* is also a major determinant of severe COVID-19 (e.g., [18, 19]). By contrast, *APOE4* is protective against hepatitis C virus-induced liver disease [20] and malaria [21].

Diverse pathogens have been reported in AD brain, ranging from bacteria to fungi to viruses [22–32]. Although it is possible that pathogen contamination might be introduced during sampling or processing, the accumulated evidence argues against contamination. The presence of bacteria and fungi in AD brain has been confirmed by multiple methods including DNA-based studies, proteomics, immunohistochemistry, and peptidoglycan analysis; moreover, hyphal structures were detected in brain that are thought to take weeks, months, or even longer to develop [27, 33], arguing against contamination. Brain expression levels of C-reactive protein (CRP), a marker of infection, are increased 20-fold in AD brain tissue versus controls [34], but not in serum (e.g., [35]). These changes could not be produced by postmortem contamination. The brain also expresses other antimicrobial factors such as chitinases that defend against fungal infection [36], and these are also upregulated in AD brain [37–40]. In one study of AD versus control brain, *CHIT1* was the most highly upregulated gene [41], potentially indicative of local fungal infection. In support, the fungal cell-wall component chitin has also been reported in AD brain [42–44] but was not found in control brain [45]. In addition, bacteria in AD brain have been further characterized by direct culture *in vitro* [46, 47], and bacterial infection could be transmitted by intracerebral inoculation of mice with human brain material [25]. Although each of these studies may be open to challenge, the combined weight of evidence argues that the brain houses its own microbiome, and that infection may contribute to the neuroinflammation and neurodegeneration seen in AD.

Adding to the plausibility that infections might contribute to dementia, there have been a series of clinical cases in which dementia was found to be directly associated with fungal, bacterial, or viral infections, and in some cases dementia remitted following appropriate antimicrobial intervention (reviewed in [14]). Moreover, it has been argued that aging *per se*—the greatest risk factor for all types of dementia—is associated with decline of the immune system (immunosenescence) that predisposes to diverse infectious disorders including those of the central nervous system, as substantiated by increased levels of microbes in brain of elderly individuals [2].

PROTECTIVE EFFECTS OF BCG AGAINST DEMENTIA

Given the possible role of infectious agents in neurodegenerative conditions, BCG and other vaccines (and sometimes classic adjuvants such as alum) have been studied for their potential protective effects against AD. The protective effects of vaccines such as BCG against AD first came to the fore in long-term follow-up studies of bladder cancer patients where instillation of BCG into the bladder is now the standard of care [48]. In a recent report, a total of 1,371 patients diagnosed with bladder cancer (mean age 68 years at diagnosis) were studied, of which 64% were treated with BCG. Medical records for the next three decades were used to determine the incidence of AD in BCG-treated versus untreated patients, and it was discovered that the rate of AD was reduced by a factor of four in BCG-treated individuals [49].

The protective effects of BCG against AD have now been independently confirmed, although the extent of protection is generally lower than was first observed, but this could reflect differences in the vaccine strains employed (Fig. 1C in Part I of this work [50]). Studies of BCG as a preventative therapy for AD are summarized in Table 1. In addition, several other (non-BCG) vaccines have also been studied,

and reports of protection are summarized in Table 2. A dose-dependent effect of BCG was suggested in the Seattle study [51], and in New York recipients of both initial and maintenance BCG had a further lowered the incidence of AD or other dementia [hazard ratio (HR) 0.23; CI 0.06–0.96] versus patients who did not receive BCG [52].

A meta-analysis of the BCG versus dementia in bladder cancer patients has recently been published [53]. Although there was some heterogeneity, when the different studies were weighted and pooled, the combined hazard ratio was 0.55 (CI 0.42–0.73), arguing for a 45% reduction in dementia incidence in bladder cancer patients treated with BCG. There are, however, some caveats. First, all these studies are retrospective in nature. Second, it was not possible to determine from the clinicians involved why some patients received BCG whereas others did not. One possibility is that patients not treated with BCG suffered from more severe disease that had spread to other tissues, and the physicians may have worried that topical (intravesicular) application would be ineffective. These patients potentially had shorter lifespans and hence were less likely to develop dementia during the recording period. In addition, potentially more severe comorbidities (in the untreated arms) could have predisposed to dementia development. Nevertheless, rates of BCG administration in bladder cancer patients varied from 23% to 64% (Table 1), indicating that the decision is more dependent on the treating center than on the patient. There was no relationship between the proportion of patients treated and the extent of protection ($R^2 = 0.0391$).

Protection extended to AD biomarkers, and BCG (ID) was reported to have positive effects on amyloid burden in healthy volunteers. A group of 49 immunocompetent BCG-naïve individuals with a family history of 'dementia' and 50–80 years of age completed the study (NCT04449926). The mass spectrometry-based plasma amyloid 42/40 ratio combined with the age and *APOE* genotype of each individual was used to generate an amyloid probability score (APS) that identifies low, intermediate, or high risk of having a PET scan positive for cerebral amyloid. This has been found to be highly predictive of amyloid PET status, and even more so when age and *APOE* status are added [54, 55]. In this group of volunteers, 34 were low risk and 15 moderate to high risk. They were given BCG and a booster. In those who completed 9 months following vaccination, their APS scores revealed a reduction in all the risk groups, but of different statistical significances: low-risk group ($p = 0.37$), intermediate-risk group ($p = 0.13$), and the high-risk group (statistically significant, $p = 0.016$). Greater benefit was seen in younger participants and those with the highest risk [56].

Overview

The key findings from Tables 1 and 2 may be summarized as follows. First, the level of BCG protection against AD is generally higher (mean 47% reduction averaged over 6 studies, not adjusted for sample size; 45% in the published meta-analysis) than for other vaccines (mean 29% averaged over all studies listed in Table 2). One non-BCG vaccine stands out: the herpes zoster recombinant vaccine Shingrix administered alone in one study gave a 72% reduction in dementia rates, whereas the live attenuated vaccine Zostavax gave only a 7% reduction ([57] and Table 2). The authors point out that Shingrix (unlike Zostavax) contains the dual adjuvant system AS01 (Box 2), and it is possible that the adjuvant underlies the increased efficacy of the vaccine. However, this is based on a single study, and future work will be necessary to determine whether BCG (over 70% protection in some studies) is comparable or better than Shingrix and/or AS01 adjuvant in terms of efficacy and, most importantly, in duration of protection. In addition, because different BCG vaccine substrains differ in their genetic makeup (Fig. 1C in Part I [50]), it would be helpful to evaluate whether they differ in efficacy and, if they do, which isolate is most effective. We remark that chemical adjuvants may have considerable efficacy in the short term, but this is likely to decline, in contrast to live agents such as BCG that arguably may persist over a lifetime.

Although most of the studies listed here are epidemiological, and some results are discordant, the combined weight of evidence is highly suggestive. However, protection is generally incomplete, and, as a rule of thumb only, rates of prevention/protection are often in the broad range of 10–50% (Tables 1 and 2), to be compared against COVID vaccines that protect against severe SARS-CoV-19 infection at ∼90%, diphtheria vaccine confers 97% protection, and tetanus vaccine is virtually 100% effective against tetanus. Even so, for diseases such as AD where we have no effective treatment, a success rate of even 10% would be a remarkable achievement, and would undoubtedly outperform the marginal benefits obtained with other anti-AD therapeutics.

Table 1
Bacille Calmette–Guérin (BCG) vaccination and protection against dementia[a,b,c,d]

Institution	Source	Reduction in dementia	Comment[e]	Refs
Hebrew University and Hadassah Medical Center (Israel)	Patient database of bladder cancer, 1,371 individuals, 64% treated with BCG	HR=0.28 (78% reduction)	Data from a single hospital, mean age 68 years, with a mean of 8 years follow-up	[49]
Massachusetts General Brigham Health Care (USA)	Patient database of bladder cancer, 6,467 individuals, 52% treated with BCG	HR over total = 0.8 (20% reduction), and in those over 70 years = 0.7 (30% reduction)	Seven-year follow-up of patients mean age 70 years. There was also a decreased risk of death in patients without an earlier diagnosis of AD	[92]
New York University, Montefiore Hospital (USA)	Patient database of bladder cancer, 12,90 individuals, 25% treated with BCG	HR=0.41 (59% reduction). There was a dose-dependent effect (HR 0.23, CI 0.06–0.96 in individuals receiving both induction and maintenance BCG)	Racially diverse; mean age 70 years, with 3 years follow-up. There was an apparent gender effect with women being less responsive	[52]
Clalit Health Services data (USA)	6,724 individuals with bladder cancer, 24% treated with BCG	The HMO data showed an HR of 0.79 (28% reduction)	Mean age 74 years, with a mean follow-up of 7 years. Parkinson's disease showed a reduction of 28% with BCG	[93][f]
Hebrew University and Hadassah Medical Center (Israel)	700 individuals with bladder cancer, 58% treated with BCG	HR=0.31 (69% reduction)	Mean age 73 years, with a mean follow-up of 6.3 years	[93]
University of Washington School of Medicine, Seattle (USA)	SEER database of bladder cancer, 26 584 individuals, 51% treated with BCG	HR = 0.73 (27% reduction)	Mean age 78 years, follow-up not specified. Results were dose-dependent	[51]

[a]A summary of the immune reactions in intravesicular BCG and those involved in prevention of recurrences can be found in [94, 95]. [b]CI, 95% confidence interval; HMO, Health Maintenance Organization; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results (National Institutes of Health, USA). [c]A meta-analysis of the influence of BCG on dementia rates has recently appeared [53]. [d]Where multiple datapoints were presented, means are given. Not all data from all reports are fully internally consistent/accurate, but the discrepancies are small. [e]Vaccine strains: there is uncertainty about the specific vaccine strains employed. Gofrit *et al.* [49] used OncoTICE BCG 12.5 mg per vial. TICE was developed at the University of Illinois from a strain developed at the Pasteur Institute; note, TICE is distinct from Pasteur (Fig. 1 in Part I of this work [50]). In [51, 52, 92], the strain was not specified, whereas in [93] the strain is inferred to be OncoTICE. [f]The study by Klinger et al. [93] reported (in the Supplementary Material) a further 4,760 bladder cancer patients of median age 69 years, of whom 315 were BCG treated (7%). There were 132 AD cases in the untreated group, but none in the BCG group. Because this would point to a HR of zero, this result has been omitted from the main table. However, it provides further support for the protective efficacy of BCG.

IS THE PROTECTIVE EFFECT AGAINST DEMENTIA REAL?

There is an obvious caveat to epidemiological studies of vaccine recipients. Dementia-related brain pathology is thought to develop gradually, probably over decades. For this reason, individuals electing to receive a vaccine of any type could plausibly be less likely to be in the early preclinical stages of cognitive impairment, meaning that their likelihood of developing dementia within the study period should be reduced. Conversely, it could also be argued that individuals at risk of dementia have already been earmarked by health authorities, who would be vigilant about arranging their vaccination, whereas fully healthy/active individuals might feel that vaccination (for example against influenza or shingles) is an unnecessary call on their time. Some of the confounding factors have been debated in a thoughtful commentary [58]. Importantly, of ∼20 studies on BCG and other vaccines, one large study from McGill university [59] reported an increased—not decreased—risk of dementia in (non-BCG) vaccine recipients (Table 2), which they attributed to unspecified confounding and detection bias. The reasons for this discordant result are not known, noting that BCG was not addressed in this study.

Do vaccines actually protect against dementia development? Regarding potential bias, vaccines are medications that require prescription and administration, and in the study of Wilkinson et al. of a total of 744 medications, 217 were associated with increased dementia risk, whereas only 4 were associated with reduced dementia risk, and all were vaccines (Table 2)

Table 2
Vaccination and dementia rates in individuals receiving non-BCG vaccines[a,b,c]

Vaccine	HR dementia versus control (% reduction)	95% Confidence interval	Refs
Single vaccination			
Diphtheria	0.41 (59%)	0.27–0.62	[96]
	0.79 (21%)	NA	[60]
Hepatitis A	0.78 (22%)	NA	[60]
Herpes zoster	0.81 (19%)	0.66–0.99	[97]
	0.76 (24%)[d]	NA	[98]
	0.69 (31%)	0.67–0.72	[99, 100]
	0.72 (28%)	0.69–0.75	[101]
	0.73 (27%)	NA	[60]
Herpes zoster (Zostavax)	0.93 (7%)	0.91–0.95	[57]
Herpes zoster (Shingrix)	0.28 (72%)	0.26–0.30	[57]
Herpes zoster (non-Shingrix)	0.78 (28%)	0.77–0.79	[102]
Influenza	0.75 (25%)	0.54–1.04	[96]
	1.09 (9% increase)	0.94–1.26	[103]
	0.83 (17%)	NA	[104]
	0.68 (32%)	0.62–0.74	[105]
	0.67 (33%)	0.61–0.74	[106]
	0.86 (14%)	0.83–0.88	[107]
	0.60 (40%)	0.59–0.61	[108]
	1.11 (11% increase)	NA	[60]
Pneumococcus	0.73 27%)	0.71–0.74	[57]
Poliomyelitis	0.60 (40%)	0.37–0.99	[96]
Tdap	0.58 (42%)	0.54–0.63	[109]
Tdap or Td	0.71 (29%)	0.69–0.72	[57]
Typhoid	0.80 (20%)	NA	[60]
Multiple vaccination			
Hepatitis A plus typhoid	0.68 (32%)	NA	[60]
Influenza			
2–3 vaccinations	0.80 (20%)	0.70–0.92	[103]
4 or more	0.38 (62%)	0.32–0.43	[103]
2 vaccinations	0.99 (1%)	0.95–1.04	[107]
3–5 vaccinations	0.97 (3%)	0.93–1.00	[107]
>6 vaccines	0.88 (12%)	0.83–0.94	[107]
Herpes zoster plus Tdap			
Dual vaccination (VHA)	0.50 (50%)	0.43–0.59	[110]
Dual vaccination (MarketScan)	0.58 (48%)	0.38–0.89	[110]
Herpes zoster			
Shingrix 2 doses	0.23 (77%)	0.21–0.26	[57]
Shingrix 2 doses plus Zostavax	0.14 (86%)	0.11–0.18	[57]
Alum adjuvant			
IMM-AD04	Reduced rate of cognitive decline	Effect size stated to be 17% ($p = 0.0067$)	[67]
Contradictory data			
Any vaccine (influenza, pneumococcus, shingles, diphtheria, tetanus, pertussis; BCG was not included in this study)	1.37 (37% increase)	1.35–1.39	[59]

[a]Studies are typically in the population aged 65 years and above. Follow-up times are very variable, but are generally in the range of ∼5 years. [b]HR, hazard ratio; NA, not available; Td, tetanus and diphtheria vaccine; Tdap, combined tetanus, diphtheria, and pertussis vaccine; VHA, Veterans Health Administration. [c]Three meta-analyses have recently been published [111–113]. [d]Memory loss/social disorientation as a proxy for dementia.

[60]. It remains unclear why only vaccines (and not the hundreds of other medications) would be subject to inferred confounding and detection bias. In addition, studies on BCG have focused on bladder cancer patients (where BCG vaccination is the standard of care), and whether to administer BCG is the decision of the clinician, making it less likely that bias has inadvertently been introduced that would influence dementia development years later. Moreover, a randomized clinical trial of BCG (where bias is likely

to be minimal) found that vaccination offers significant protection against respiratory infections in the elderly [1]. Further studies will be essential, but the weight of the evidence to date argues that BCG is very likely to have broad-spectrum protective effects against multiple disorders including dementia.

ADJUVANTS AND ALZHEIMER'S DISEASE: COULD BCG BE REPLACED BY KEY MOLECULES SUCH AS MURAMYL DIPEPTIDE (MDP)?

In Part I, we reviewed evidence that mycobacteria such as *M. tuberculosis*, *M. bovis*, and BCG can have broad stimulatory effects on the immune system, and that specific mycobacterial molecules such as MDP can replace the mycobacterial component in the best adjuvant to date, Freund's complete adjuvant (FCA) [50]. Given the positive protective effects of BCG against diverse conditions including bladder cancer, and now AD, could BCG be replaced by MDP—the major immunopotentiating cell wall component of mycobacteria?

There are no convincing answers to this question so far. Regarding human bladder cancer, we know of no clinical study that has sought to replace BCG by MDP or FCA (although some animal trials have been performed). However, MDP analogs are being studied for their potential anticancer activities (reviewed in [61]); these include muramyltripeptide phosphatidylethanolamine (MTP-PE, mifamurtide) embedded in liposomes (Mifamurtide/Mepact) that is widely used in osteosarcoma adjuvant therapy [62]. Clinical trials of MDP analogs have been reviewed [63].

By contrast, we have glimpses that molecular adjuvants might be of significant benefit in AD. MDP administration in AD model mice is reported to delay AD-related pathology [64]. Another adjuvant molecule, the CpG oligodeoxynucleotide 2006 (CpG ODN), has shown promise in mouse AD models [65] and produced favorable reductions in naturally occurring amyloid pathology in elderly squirrel monkeys [66]; clinical trials are planned in New York (NCT05606341). Another adjuvant molecule, IMM-AD04 alum (Box 2), was reported to slow cognitive decline in AD patients ([67] and Table 2). Note also the protective effects of adjuvanted Shingrix vaccine (Table 2) that might be due to the vaccine adjuvant rather than to the vaccine antigens (discussed earlier).

Although part of the immune boosting effects of mycobacteria can be attributed to MDP, and two receptors, when activated, promote diverse immunological responses, muramyl peptides are likely to operate in synergy with other mycobacterial PAMPS (Box 3 in Part I [50]; see also [68]) such as trehalose dimycolate [69, 70] that can independently stimulate the immune system, potentially arguing that BCG itself, rather than MDP or other single adjuvants, may be best way forward. Moreover, the existence of different BCG substrains (Fig. 1 in Part I [50]), which are likely to differ in efficacy, means that comparative studies will be necessary to select the best isolate, although this could potentially be masked by differences in culture and manufacture conditions (batch effects) and in formulation (reviewed in [71]).

CONCLUDING REMARKS: PERSPECTIVES FOR BCG AS A GENERIC PROPHYLACTIC IMMUNOPROTECTANT

Powerful immunoenhancement induced by BCG has been widely reported, and BCG protection may extend beyond traditional infectious diseases such as pneumonia to cancers and dementia. Should BCG become part of the routine armamentarium of medical practitioners? We recognize that intravesicular administration of BCG (as in bladder cancer) is certainly a non-starter as a general public health measure. Today even a jab can be contentious, and an oral vaccine would be more acceptable. However, the majority of orally administered BCG bacteria are inactivated in the gut before reaching intestinal lymphoid tissue [72], and an oral 'BCG pill' may require reformulation to protect it against the harsh environment of the stomach.

What would it take to bring an oral general immune booster onto the public health agenda? Calmette in his 1931 article concluded with 'What doctor, what sanitary authority, knowing these facts, and with all the necessary information now available, would deliberately refuse to apply this simple method of defense against the most virulent of all human diseases?' [73]. TB still reigns dominant as a 'most virulent' disease, and Calmette's BCG could be refashioned as an oral pill that is 'simple' to take. Moreover, the evidence argues that BCG confers a measure of protection against age-related diseases including dementia. Despite this, little attention has been paid to the potential utility of BCG in defending against AD. This is perhaps surprising given that drug development in

AD, generally based on removing Aβ or preventing its formation, has met failure after failure [74]. There have been potential exceptions, such as lecanemab that was recently granted accelerated approval by the FDA for AD, but such drugs are highly controversial, enormously expensive (estimated cost $25,000 + per year per patient), and their clinical benefits are so modest (if at all) that they may not be clinically actionable (e.g., [75–77]). Vaccines such as BCG cost trivial amounts by comparison, but there has been no political will to advance this area of research.

However, two trials of BCG in dementia are about to start or are ongoing. The first (PI Steven E Arnold; NCT04507126) is based at Massachusetts General Hospital and will focus on BCG effects on biomarkers of AD. The second (PI Tamir Ben-Hur) at Hadassah Hospital will follow a cohort of cognitively intact high p-tau individuals who will initially be given BCG (ID), a booster at 1 month, and another at 1 year. Follow-up will include cognitive tests.

A word of caution: many individuals are already immunologically reactive to mycobacterial species, and BCG inoculation could potentially produce adverse results including intense inflammation at the site of administration in individuals who already have strong anti-*Mycobacterium* immunity. For this reason, it may be necessary to perform a tuberculin [78, 79] or interferon-γ (IFN-γ) release assay (IGRA) test such as QuantiFERON and T-SPOT TB test. IGRAs measure the release of IFN-γ from a fresh blood sample in response to synthetic *M. tuberculosis* antigen. These have the advantage that they are specific for *M. tuberculosis*, and individuals in receipt of BCG vaccination are said not to give a false positive response (Centers for Disease Control; https://www.cdc.gov/tb/publications/factsheets/general/tb.pdf). Although there was a high level of agreement between QuantiFERON and T-SPOT, they are commonly discordant with the tuberculin skin test [80] and can give false negatives even in individuals with active tuberculosis [81].

Nevertheless, these concerns may not be substantial. In studies on bladder cancer patients no preliminary testing for anti-*Mycobacterium* immunity was performed, and it would be of great interest to determine whether tuberculin status influences both bladder cancer remission and later dementia protection in recipients of intravesicular BCG. Centrally, concerns about pre-existing mycobacterial immunity may be unfounded because repeat administration of BCG appeared to have no ill effects, as suggested by several repeat inoculation studies (e.g., [52, 82, 83]).

Worldwide, BCG is most frequently administered to infants, and only a low frequency of adverse effects has been reported, although immunodeficient and HIV-infected children can be at risk of disseminated infection [84]. However, adults are the target population in the context of dementia prevention. In studies on individuals aged 19–74 years, abscess and/or lymphadenopathy was seen in ∼3% of vaccine recipients, that generally resolved upon treatment [82, 83]. Nevertheless, given suggestions that elderly individuals, particularly those at risk of AD, may have some degree of immune decline [2], close monitoring of vaccine recipients is warranted.

Looking to the future, could we engineer a 'super-BCG' that is even more effective? BCG could provide a framework for even more potent engineered immunostimulants [85–88]. An obvious place to start would be to study the protective properties of different BCG strains that have arisen over the past century (Fig. 1 in Part I of this work [50]).

To conclude, mankind evolved in close contact with diverse microorganisms, including mycobacteria (Box 1 in [50]). There are notable cases where infections can have beneficial effects on both physiology and, importantly, cognition (reviewed in [89]), and we raise a more general question of whether, as in the gut, a healthy microbiome in immune tissues and brain could ward off damaging infections by rewiring the immune system or through direct competition. Recent (but controversial) reports that gastrointestinal tract infusion of select gut bacteria (notably those from young mice, and of the same group as mycobacteria) into experimental animals can promote immune system function [90, 91] suggests that we are on the right track. Perhaps BCG is one such beneficial microbe?

AUTHOR CONTRIBUTIONS

Charles Leonard Greenblatt (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing); Richard Lathe (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing).

ACKNOWLEDGMENTS

We thank Janet Janbek, Shoshana Frankenburg, Tom Dow, and Brian Balin for helpful comments on

the manuscript. Cure Alzheimer's Fund is thanked for encouraging C.L.G. to think about how BCG works.

FUNDING

The authors have no funding to report.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

NOTE ADDED IN PRESS

A recent study, by Wang and colleagues in Sweden, on the potential link between BCG vaccination confirms the protective effects of BCG, notably in the population aged 75 years or above, but also highlights some complexities of interpretation.

Reference: Wang E, Hagberg O, Malmström P-U (2023) The association between BCG treatment in patients with bladder cancer and subsequent risk of developing Alzheimer and other dementia – a Swedish nationwide cohort study from 1997 to 2019. PLoS One 18, e0292174.

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