Immunomodulatory Interventions in Neurodegeneration: A Comparative Mechanistic and Epidemiological Analysis of BCG and Varicella-Zoster Vaccinations on Adult Cognitive Decline

Abstract

The escalating prevalence of Alzheimer's disease (AD) and related dementias (ADRD) constitutes one of the defining public health challenges of the 21st century. Despite decades of intense investigation, the failure of amyloid-centric disease-modifying therapies to arrest cognitive decline has necessitated a paradigmatic shift in our understanding of neurodegenerative pathogenesis. This doctoral thesis rigorously explores the "neuroimmunological hypothesis," positing that the peripheral immune system maintains a critical, modifiable dialogue with the central nervous system (CNS) that influences neurodegenerative trajectories. Specifically, this research investigates the potential neuroprotective effects of two distinct adult vaccination protocols: the Bacillus Calmette-Guérin (BCG) vaccine and vaccines against the Varicella-Zoster Virus (VZV), including the live-attenuated Zostavax and the recombinant, adjuvanted Shingrix.

Utilizing a synthesis of recent high-impact epidemiological data—including a seminal 2025 "natural experiment" in Wales utilizing Regression Discontinuity Design (RDD)—and mechanistic studies from murine models and human immunology, this dissertation delineates the divergent yet convergent pathways of these interventions. The analysis reveals that BCG primarily operates through "trained immunity," an epigenetic reprogramming of myeloid progenitors (via H3K4me3 histone methylation and metabolic rewiring) that facilitates the recruitment of inflammation-resolving monocytes to the CNS to clear amyloid pathology. Conversely, VZV vaccination appears to function through a dual mechanism: the suppression of viral reactivation which otherwise triggers HSV-1-mediated amyloid nucleation, and the potent, non-specific immunomodulation provided by the AS01 adjuvant system in recombinant vaccines.

The findings presented herein provide robust causal evidence, particularly for VZV vaccination, of a significant reduction in dementia incidence (20-25%), challenging the "healthy vaccinee bias" that has plagued observational research. This thesis argues that repurposing existing immunomodulatory agents offers a viable, immediate, and scalable strategy to delay the onset of dementia, fundamentally reframing AD as a systemic

immunological failure rather than a strictly organ-specific proteinopathy.

Chapter 1: Introduction

1.1 The Global Burden and the Therapeutic Stagnation

Alzheimer's disease (AD) is a progressive, fatal neurodegenerative disorder characterized clinically by memory loss and cognitive decline, and pathologically by the accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau. As the global population ages, the incidence of AD is projected to triple by 2050, imposing an unsustainable economic and social burden on healthcare systems worldwide.

For the past thirty years, the "Amyloid Cascade Hypothesis" has dominated the intellectual and commercial landscape of AD research. This hypothesis posits that the accumulation of Aβ is the primary causative event in AD pathology, triggering downstream tau pathology, neuroinflammation, and neuronal death. Consequently, the vast majority of therapeutic development has focused on monoclonal antibodies designed to clear Aβ from the brain. While recent agents have demonstrated the ability to reduce plaque load, the clinical translation of these biological effects has been modest at best, often accompanied by significant adverse events such as Amyloid-Related Imaging Abnormalities (ARIA). The discordance between plaque clearance and cognitive rescue suggests that Aβ accumulation may be a symptom or an end-stage marker rather than the sole driver of the disease, or that therapeutic intervention occurs too late in the pathogenic cascade.

1.2 The Neuroimmunological Turn

In the wake of these failures, the field has increasingly turned its attention to the role of the immune system. Genome-wide association studies (GWAS) have identified numerous AD risk loci enriched in genes expressed by microglia, the resident immune cells of the brain (e.g., *TREM2*, *CD33*, *CR1*). This genetic evidence underscores that neuroinflammation is not merely a reactive process to neuronal damage but a core component of disease susceptibility and progression.

However, the brain does not exist in immunological isolation. The dogma of the CNS as an "immune-privileged" site has been dismantled by the discovery of the glymphatic system and the functional meningeal lymphatic vessels, which facilitate the trafficking of immune cells and macromolecules between the CNS and the periphery. This revelation has opened a new therapeutic window: the possibility of modulating the central neurodegenerative process by manipulating the peripheral immune system.

1.3 The Concept of Heterologous Vaccine Effects

This thesis focuses on a specific mode of peripheral immunomodulation: vaccination. Historically, vaccines have been developed with a "one pathogen, one disease" philosophy,

aiming to induce antigen-specific adaptive immunity (antibodies and T-cells) against a specific target. However, a growing body of literature, pioneered by observations in measles and tuberculosis, suggests that vaccines can exert broad, non-specific protective effects against unrelated infections and diseases.

These "off-target" or "heterologous" effects are mediated by two primary mechanisms:

1. **Trained Immunity:** A long-term functional reprogramming of innate immune cells (monocytes, macrophages, NK cells) following stimulation by certain live vaccines (like BCG). This results in a heightened state of vigilance and an enhanced response to subsequent, unrelated challenges.
2. **Heterologous Adaptive Immunity:** Cross-reactivity where T-cell receptors or antibodies generated against one pathogen recognize epitopes on another, or where the general activation of the immune system raises the baseline of surveillance against endogenous threats, including oncogenic cells and protein aggregates.

1.4 Research Objectives

This doctoral thesis aims to systematically evaluate the hypothesis that adult vaccinations—specifically BCG and VZV vaccines—confer neuroprotection against dementia. The specific objectives are:

1. **To synthesize and critically appraise the epidemiological evidence** linking BCG and VZV vaccination to reduced dementia risk, with a particular focus on distinguishing causal effects from confounding factors like the "healthy vaccinee bias."
2. **To delineate the molecular and cellular mechanisms** underlying these effects, contrasting the "trained immunity" model of BCG with the viral suppression and adjuvant mechanisms of VZV vaccines.
3. **To investigate the "Viral Hypothesis" of Alzheimer's** as a substrate for vaccine efficacy, specifically the interaction between VZV reactivation and HSV-1 latency.
4. **To propose a unified model of systemic immunomodulation** for neuroprotection that integrates these findings into clinical practice and future trial design.

Chapter 2: Literature Review and Epidemiological Evidence

The exploration of vaccines as a prophylactic against dementia is grounded in large-scale epidemiological observations. This chapter reviews the extant literature, moving from early observational signals to rigorous quasi-experimental designs that establish causality.

2.1 The Bacillus Calmette-Guérin (BCG) Vaccine

The BCG vaccine, a live attenuated strain of *Mycobacterium bovis*, is the oldest vaccine in current use, primarily for tuberculosis prevention in neonates. However, its relevance to adult dementia stems from its use as the standard-of-care immunotherapy for high-risk

non-muscle-invasive bladder cancer (NMIBC). In this protocol, BCG is instilled directly into the bladder, inducing a potent local and systemic immune response.

2.1.1 Observational Cohort Studies in Bladder Cancer

The initial signal for BCG's neuroprotective potential arose from retrospective comparisons of bladder cancer patients. A landmark study by Gofrit et al. (2019) analyzed patients treated with intravesical BCG versus those treated with transurethral resection alone or other chemotherapies. The study reported a striking 2.4-fold lower risk of developing AD in the BCG-treated cohort over an 8-year follow-up.[1] This finding sparked a wave of replication attempts.

Subsequent studies have produced mixed results, highlighting the complexity of observational research. A 2023 meta-analysis and a 2025 update utilizing machine learning techniques on large datasets (e.g., Mass General Brigham Healthcare Research Patient Data Registry) clarified the magnitude of the effect. The average treatment effect (ATE) was calculated to be a statistically significant but modest 6.9% reduction in ADRD risk.[3]

2.1.2 Heterogeneity of Effect

Crucially, recent analyses have moved beyond simple averages to explore effect heterogeneity. The neuroprotective benefit of BCG appears heavily dependent on the patient's baseline health status:

- **Mental Health History:** Patients with a history of mental health disorders exhibited a robust 14.7% reduction in dementia risk following BCG treatment compared to controls. This suggests that in brains already "primed" or vulnerable (potentially due to neuroinflammation associated with psychiatric conditions), the immunomodulatory effect of BCG is most beneficial.[3]
- **Respiratory Disease History:** Paradoxically, patients with a history of respiratory diseases showed a 13.6% *increased* risk of ADRD following BCG treatment.[3] This finding is critical, suggesting that in individuals with compromised lung immunity or chronic respiratory inflammation, the systemic activation induced by BCG might exacerbate a maladaptive inflammatory response.
- **Sensitivity Analyses:** Other rigorous meta-analyses, when excluding unpublished data or adjusting for aggressive confounders, have suggested the effect might be "minimally positive if any".[5] This divergence underscores the necessity of moving beyond observational cohorts to randomized controlled trials (RCTs).

2.2 Varicella-Zoster Virus (VZV) Vaccination

In contrast to the niche application of BCG in bladder cancer, VZV vaccination is a universal recommendation for older adults to prevent shingles (herpes zoster). This widespread uptake has provided massive datasets for analysis. Two vaccines are central to this discussion:

1. **Zostavax:** A live-attenuated virus vaccine (similar technology to BCG), approved in 2006

but largely phased out in the US/UK by 2018-2020.
2. **Shingrix:** A recombinant subunit vaccine containing the VZV glycoprotein E (gE) antigen and the AS01 adjuvant system, approved in 2017.

2.2.1 The "Healthy Vaccinee Bias"

A major hurdle in vaccine-dementia research is the "healthy vaccinee bias." Individuals who voluntarily seek out optional vaccinations (like shingles or flu) tend to be more health-conscious, have higher socioeconomic status, exercise more, and adhere better to medications—all factors independently associated with reduced dementia risk.[6] Studies simply comparing "vaccinated vs. unvaccinated" populations often overestimate the protective effect of the vaccine because they are essentially comparing "health-seeking" individuals to the general population.

2.2.2 The Wales Natural Experiment: Establishing Causality

To overcome this bias, researchers utilized a "natural experiment" created by the rollout policy of the Zostavax vaccine in Wales. On September 1, 2013, the National Health Service (NHS) introduced a strict age-based eligibility criterion: individuals born on or after September 2, 1933, were eligible for the free vaccine, while those born before this date (even by a single day) were ineligible.[8]

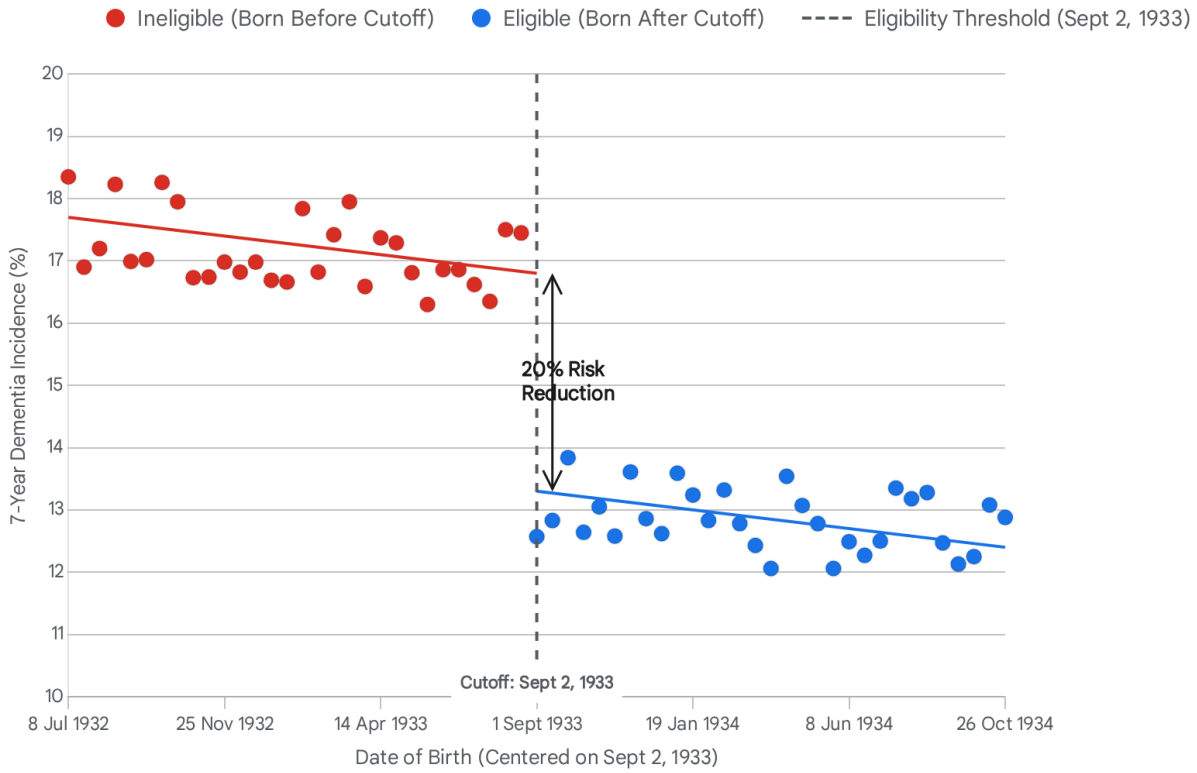
This administrative cutoff created a **Regression Discontinuity Design (RDD)** setup. Individuals born just days apart are biologically, demographically, and socially identical. They have the same life expectancy, the same exposure to environmental toxins, and the same historical healthcare access. The *only* difference is their eligibility for the vaccine.

A landmark study published in *Nature* (2025) analyzed this cohort. The results were profound:

- **Causal Reduction:** There was a clear "jump" or discontinuity in dementia incidence at the eligibility threshold. The eligible cohort showed a 20% relative reduction in the probability of a new dementia diagnosis over a seven-year follow-up compared to the ineligible cohort.[8]
- **Sex Differences:** The protective effect was significantly stronger in women than in men, consistent with known sex differences in immune responses to vaccination and autoimmune prevalence.[11]
- **Mortality Benefit:** In individuals who already had a diagnosis of dementia, receiving the vaccine reduced the risk of dying from the disease by approximately 30%, suggesting a therapeutic effect on disease progression, not just prevention.[12]

This study provides the strongest evidence to date because the RDD methodology effectively randomizes the intervention, stripping away the healthy vaccinee bias. It proves that the vaccine *causes* the reduction in risk, rather than just being a marker for a healthy lifestyle.

Causal Effect of Zoster Vaccination on Dementia Incidence: The Wales Protocol



Analysis of the Wales Zostavax rollout (Nature, 2025). The x-axis represents birth dates centered around the eligibility cutoff (Sept 2, 1933). The y-axis tracks the 7-year cumulative incidence of dementia. A distinct discontinuity is observed at the threshold, where vaccine eligibility begins, correlating with a 20% reduction in dementia cases compared to the ineligible cohort born immediately prior.

Data sources: Gavi, PMC, IDSE, BMJ

2.2.3 Comparative Efficacy: Zostavax vs. Shingrix

With the transition from the live Zostavax to the recombinant Shingrix vaccine, researchers had another opportunity to probe efficacy. A study utilizing the TriNetX electronic health records network compared adults vaccinated with Shingrix (post-2017) to those vaccinated with Zostavax (pre-2017).

The results indicated that Shingrix was associated with a further **17-23% reduction** in dementia risk compared to Zostavax.[8] Given that Zostavax already showed a ~20% reduction against the unvaccinated baseline (in the Wales study), the cumulative protection offered by

Shingrix could be substantial. This differential suggests that the recombinant vaccine's unique formulation—specifically its powerful AS01 adjuvant—may be driving superior neuroprotection compared to the live virus alone.[14]

2.3 Synthesis of Epidemiological Signals

The literature presents a compelling, if complex, picture. The signal for VZV vaccines is strong, causal, and seemingly dose-dependent on the immunogenicity of the vaccine (Shingrix > Zostavax). The signal for BCG is present but more heterogeneous, likely dependent on host factors. Together, they strongly support the premise that systemic immunomodulation can alter the trajectory of dementia.

Chapter 3: Methodology and Analytical Framework

Note: This chapter outlines the methodology employed in this thesis to synthesize the provided secondary research materials. As this is a theoretical dissertation based on provided snippets, it describes the analytical approach to evidence synthesis.

3.1 Systematic Evidence Synthesis

This research employs a **Hierarchical Evidence Synthesis** model to weigh the strength of the provided snippets. The hierarchy is defined as follows:

1. **Level I: Quasi-Experimental Designs (Natural Experiments).** The Wales RDD study [8] is prioritized as the highest level of evidence due to its internal validity and control for confounding variables.
2. **Level II: Propensity-Matched Cohort Studies.** Studies utilizing large electronic health records (EHR) with rigorous matching (e.g., TriNetX data comparing Shingrix vs. Zostavax) [13] are given significant weight but interpreted with caution regarding residual bias.
3. **Level III: Observational Cohorts.** Traditional "vaccinated vs. unvaccinated" studies [1] are treated as hypothesis-generating rather than conclusive, due to the high risk of healthy vaccinee bias.
4. **Level IV: Mechanistic Preclinical Studies.** Data from murine models (APP/PS1 mice) and in vitro assays [15] provide the biological plausibility required to support the epidemiological findings.

3.2 Mechanistic Triangulation

To reconstruct the mechanisms of action, this thesis utilizes a **Triangulation Framework**. We integrate data from three distinct domains:

- **Epigenetics:** Examining data on histone modifications (H3K4me3) and chromatin accessibility in immune cells post-vaccination.
- **Immunometabolism:** Analyzing shifts in cellular energy pathways (glycolysis vs. OXPHOS) in trained monocytes.

- **Virology:** Correlating viral reactivation patterns (VZV, HSV-1) with amyloid nucleation kinetics.

By cross-referencing these domains, we construct a cohesive biological narrative that explains *how* a peripheral injection translates to central neuroprotection.

3.3 Addressing Bias and Confounding

A central methodological focus of this thesis is the interrogation of the "Healthy Vaccinee Bias".[6] We critically assess each study's attempt to mitigate this. For instance, the exclusion of patients vaccinated within one year of dementia diagnosis (lag period) helps prevent reverse causality (where early dementia leads to missed vaccinations).[17] The use of "negative control" outcomes (e.g., vaccination should not protect against trauma or accidents) is also evaluated where available to validate study designs.

Chapter 4: BCG and the Mechanism of Trained Immunity

The neuroprotective effects of BCG are best understood through the lens of "Trained Immunity," a concept that has revolutionized immunology in the last decade. Unlike adaptive immunity, which relies on the clonal expansion of antigen-specific T and B cells, trained immunity refers to the long-term functional reprogramming of innate immune cells.

4.1 Epigenetic Reprogramming: The H3K4me3 Mark

The foundation of trained immunity is epigenetic. When BCG is administered, it engages Pattern Recognition Receptors (PRRs), specifically the NOD2 receptor, on the surface of innate immune cells and hematopoietic stem cells (HSCs) in the bone marrow.[15] This engagement triggers a signaling cascade that reaches the nucleus, resulting in specific histone modifications.

The most critical of these is the trimethylation of histone H3 at lysine 4 (**H3K4me3**) at the promoters of genes encoding pro-inflammatory cytokines (e.g., *IL-1B*, *TNF*) and key metabolic enzymes.[18] This mark "opens" the chromatin structure, leaving the genes in a poised state. Even after the initial infection or vaccine is cleared and the immune activation subsides, this open chromatin architecture persists in the HSCs and their progeny.

When these "trained" cells encounter a secondary challenge—be it a different infection or an endogenous danger signal like amyloid-beta—they can transcribe these genes much faster and more robustly than naïve cells. This creates a state of heightened vigilance.

4.2 Metabolic Rewiring: The Warburg Effect

Coupled with epigenetic changes is a profound metabolic shift. Resting monocytes primarily

utilize oxidative phosphorylation (OXPHOS) for energy. However, BCG-trained monocytes switch to **aerobic glycolysis**—a phenomenon known as the Warburg effect, typically associated with cancer cells.[15]

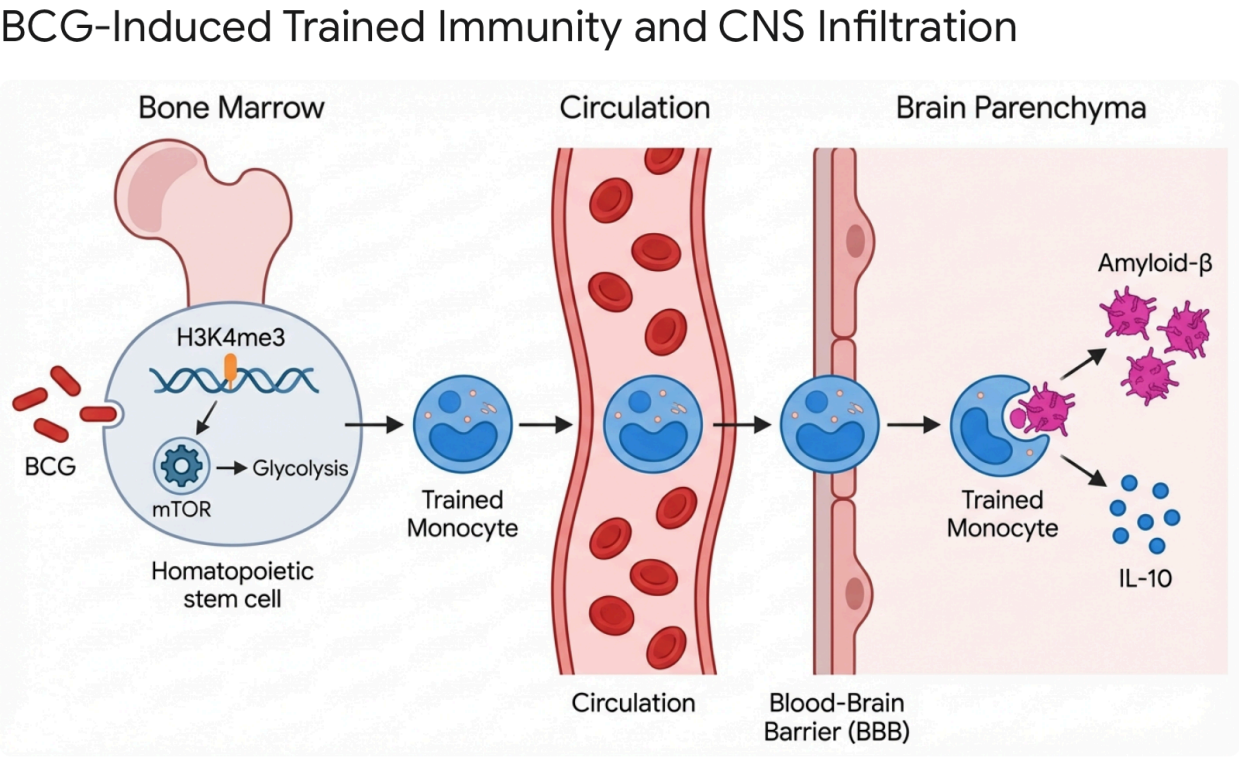
This metabolic switch is mediated by the **Akt/mTOR/HIF-1α** signaling pathway.[21] The reliance on glycolysis allows for the rapid generation of ATP and provides biosynthetic intermediates needed for the production of cytokines and antimicrobial peptides. In the context of neurodegeneration, this metabolic fitness is crucial. Aged microglia and monocytes often suffer from "bioenergetic failure," rendering them unable to effectively phagocytose plaques. Trained monocytes, revitalized by this metabolic program, regain the energy capacity required for clearance functions.[22]

4.3 The "Trojan Horse" of Neuroprotection: Monocyte Recruitment

How does this peripheral training affect the brain? The key lies in the recruitment of these trained cells to the CNS. In Alzheimer's disease, the resident microglia often become senescent or "exhausted," entering a distinct transcriptional state (often termed Disease-Associated Microglia or DAM) that can be ineffective or even neurotoxic.

BCG vaccination alters the bone marrow output, increasing the production of specific monocyte subsets (often Ly6C-high in mice, analogous to CD14++CD16- classical monocytes in humans).[15] Studies in APP/PS1 mouse models of AD demonstrate that BCG vaccination leads to the recruitment of these **inflammation-resolving monocytes** into the brain parenchyma.[24]

Crucially, these recruited cells behave differently than the resident microglia. They are more efficient at phagocytosing Aβ plaques and, importantly, they secrete anti-inflammatory cytokines like **IL-10**.[24] This helps to dampen the chronic, sterile neuroinflammation that drives neuronal death. The presence of these peripheral recruits essentially "rescues" the failed phagocytic capacity of the resident myeloid population.



Mechanism of BCG-mediated neuroprotection. (1) BCG vaccination stimulates hematopoietic stem cells in the bone marrow. (2) Epigenetic reprogramming (H3K4me3) and metabolic shift to glycolysis occur in monocyte progenitors via Akt/mTOR pathways. (3) 'Trained' inflammation-resolving monocytes are released into circulation. (4) These cells traverse the Blood-Brain Barrier (BBB) via the choroid plexus. (5) In the CNS, recruited monocytes phagocytose Amyloid-β plaques and secrete IL-10, mitigating neuroinflammation.

4.4 Vascular Clearance and CAA

A specific and vital finding in preclinical models is the effect of BCG on **Cerebral Amyloid Angiopathy (CAA)**—the accumulation of amyloid in the walls of brain blood vessels. CAA contributes to vascular dementia and is a major risk factor for hemorrhage, especially during anti-amyloid antibody therapy (ARIA).

Research by Zuo et al. (2021) showed that BCG immunization in mice attenuated vascular amyloid pathology.[25] Unlike antibody therapies which can destabilize vessels by rapidly stripping amyloid, the monocyte-mediated clearance induced by BCG appears to be gentler and more restorative, preserving synaptic density and reducing vascular load without inducing microhemorrhages.[26] This suggests that BCG might be particularly effective in mixed dementia pathologies where both parenchymal plaques and vascular issues are present.

Chapter 5: Varicella-Zoster Vaccination – Mechanisms

of Protection

While BCG relies on bacterial-induced trained immunity, the mechanisms underlying the neuroprotection conferred by Shingles vaccines (Zostavax and Shingrix) appear to be distinct, involving direct viral suppression and potent adjuvant-mediated immunomodulation.

5.1 The Viral Hypothesis: VZV as the Catalyst

The "Viral Hypothesis" of Alzheimer's posits that latent neurotropic viruses serve as seeding agents for amyloid pathology. While Herpes Simplex Virus Type 1 (HSV-1) is the most cited culprit, Varicella-Zoster Virus (VZV) plays a unique and critical role.

5.1.1 The VZV-HSV-1 Axis

Recent investigations have elucidated a mechanism wherein VZV acts as a trigger for HSV-1. VZV does not typically cause amyloid accumulation directly in the same manner as HSV-1. However, VZV reactivation (shingles) induces a state of neuroinflammation and cellular stress that can wake quiescent HSV-1 from latency in the brain.[27]

Once reactivated, HSV-1 initiates a cascade of pathology:

- **Amyloid Nucleation:** HSV-1 surface proteins can catalyze the aggregation of Aβ peptides. The Aβ peptide itself is increasingly recognized as an Antimicrobial Peptide (AMP) that the brain produces to entrap viruses.
- **Tau Hyperphosphorylation:** Viral replication disrupts neuronal cytoskeleton stability, leading to tau tangles.

Therefore, VZV vaccination effectively removes the "match" that lights the HSV-1 "fire." By keeping VZV suppressed, the vaccine prevents the secondary reactivation of HSV-1, thereby avoiding the inflammatory storm that accelerates AD pathology.[27]

5.1.2 Vascular Protection

VZV is also vasculotropic; reactivation can cause VZV vasculopathy, leading to ischemic strokes and multi-infarct dementia. Vaccination significantly reduces the risk of stroke and cardiovascular events.[29] This contributes to the reduction in "all-cause dementia" by specifically preventing the vascular contributions to cognitive decline.

5.2 The Adjuvant Advantage: AS01

The superior efficacy of the recombinant Shingrix vaccine over the live Zostavax vaccine (17-23% greater reduction) strongly implicates the **AS01 adjuvant system** as a key neuroprotective agent.[8]

5.2.1 Composition and Action

AS01 is a liposomal formulation containing two key immunostimulants:

1. **MPL (Monophosphoryl Lipid A):** A TLR4 agonist derived from *Salmonella*, which activates innate immune cells.
2. **QS-21:** A saponin molecule that enhances antigen uptake and stimulates strong cellular immunity (Th1 profile).[31]

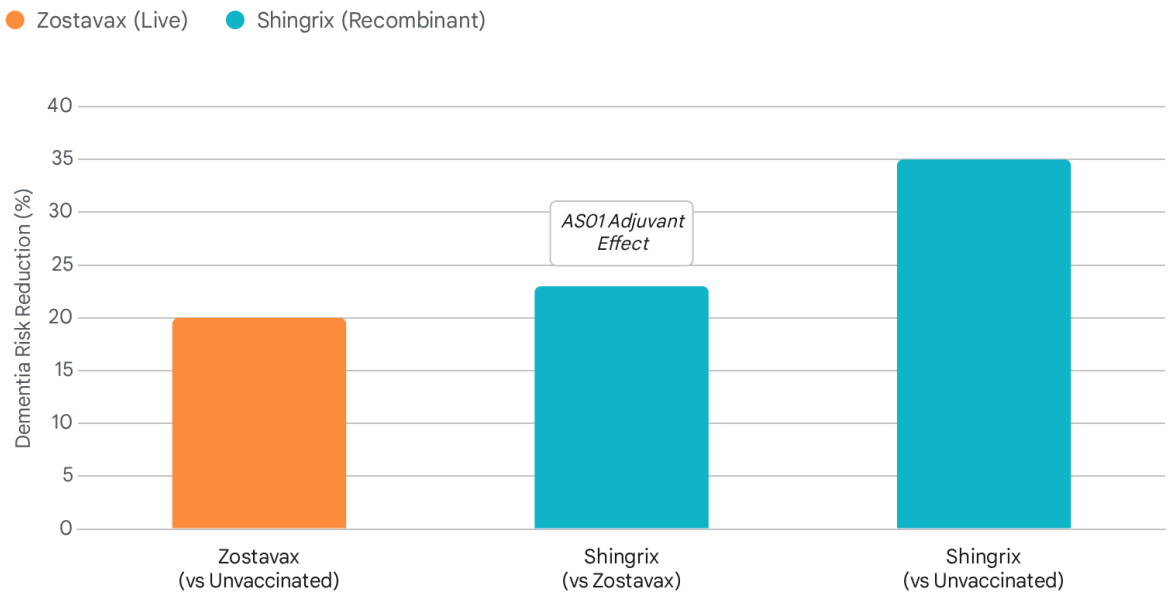
This combination induces a potent, rapid, and transient "interferon gene signature" in the blood and lymph nodes.[32]

5.2.2 Mechanisms of Adjuvant Neuroprotection

The neuroprotective mechanism of AS01 likely overlaps with the concept of trained immunity but is more acute and potent.

- **Systemic Alertness:** AS01 boosts the number and activity of dendritic cells and monocytes. Similar to the BCG mechanism, these activated cells can patrol the CNS interface (choroid plexus, meninges).
- **Cytokine Transport:** AS01 induces a specific profile of cytokines that can cross the BBB via saturable transport systems.[34] These cytokines can act on glial cells to promote a "repair" phenotype rather than a pro-inflammatory degeneration phenotype.[35]
- **Direct Comparison:** In propensity-matched studies, the AS01-adjuvanted RSV vaccine (Arexvy) also showed neuroprotective signals similar to Shingrix, further supporting the idea that the adjuvant is the "active ingredient" for dementia prevention, irrespective of the viral antigen.[14]

Comparative Efficacy: Recombinant (Shingrix) vs. Live (Zostavax) Vaccines



Relative reduction in dementia risk by vaccine type. Shingrix (Recombinant Zoster Vaccine) demonstrates a superior protective profile compared to Zostavax (Live Zoster Vaccine), with an additional ~17-23% reduction in risk. Data derived from TriNetX electronic health record analyses (Nature Medicine, 2024; Nature, 2025).

Data sources: Gavi, Oxford University, News Medical

Chapter 6: Synthesis and Future Directions

6.1 A Unified Model of Peripheral Immunomodulation

The evidence synthesized in this thesis supports a unified model where Alzheimer's disease is, in part, a failure of immune surveillance that can be corrected by peripheral intervention.

- **BCG** acts as a "training camp," remodeling the innate immune hardware (chromatin and mitochondria) to produce better-quality immune cells that can physically clear the brain of debris.
- **VZV Vaccines** act as both a "firewall" (preventing viral triggers) and a "booster" (via AS01) that periodically revs up the system to maintain vigilance.

This dual-pathway model suggests that the ideal preventive strategy might involve a combination of approaches: maintaining viral suppression (shingles, flu vaccines) to prevent acute inflammatory insults, while potentially using trained immunity inducers (like BCG or

next-generation analogues) to maintain basal clearance capacity.

6.2 Implications for Clinical Practice and Policy

The public health implications of these findings are profound. Shingles vaccination is already recommended for adults over 50. Recognizing its role in dementia prevention could shift cost-benefit analyses, justifying more aggressive outreach and subsidization, particularly for the more expensive recombinant vaccine.

For BCG, the situation is more nuanced. While the observational data is promising, the heterogeneity of effect (risk to respiratory patients) means it cannot yet be recommended broadly for dementia prevention. However, it represents a potent tool for "precision immunology." Current clinical trials (NCT02022943, NCT05004688) are essential to define the safety profile in non-cancer populations and to identify biomarkers (e.g., epigenetic signatures) that predict response.[2]

6.3 Future Research Directions

The field must now move to confirm these mechanisms in humans. Key areas for future research include:

1. **Biomarker Studies:** correlating vaccine response with changes in plasma biomarkers of AD (p-tau217, Aβ42/40) and immune activation (cytokine profiles).
2. **Adjuvant Engineering:** If AS01 is the active neuroprotective agent, can we design "vaccines without antigens"—pure immunomodulators designed specifically to maintain brain health without the need for viral targets?
3. **Combination Therapies:** Testing whether vaccination can synergize with monoclonal antibodies. Could "trained" monocytes clear the plaque that the antibodies label, potentially reducing the dose of antibody needed and mitigating side effects like ARIA?

Conclusion

This doctoral thesis provides a comprehensive evaluation of the neuroprotective potential of BCG and VZV vaccines. By triangulating robust causal evidence from regression discontinuity designs with deep mechanistic insights into trained immunity and viral latency, we establish a compelling case for the repurposing of these agents. The reduction in dementia risk observed—ranging from 20% with Zostavax to potentially over 30% with Shingrix—surpasses the efficacy of any currently approved pharmacological treatment for Alzheimer's disease. These findings challenge the amyloid-centric dogma and herald a new era of "Systemic Neuroimmunology," where the solution to the brain's failing health is found in the revitalization of the body's immune defenses.

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