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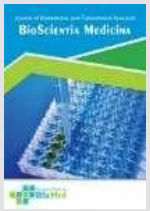

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Fatal Disseminated Tuberculosis in Vaccinated Children with Failed BCG Scar Formation: A Clinical-Pathological Correlation and Immunological Review

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A B S T R A C T

Background: The Bacillus Calmette-Guérin (BCG) vaccine remains the cornerstone of preventative strategies against severe pediatric tuberculosis (TB), specifically disseminated forms such as miliary TB and tuberculous meningitis (TBM). While the formation of a cutaneous scar is historically viewed as a surrogate marker for successful vaccine uptake and delayed-type hypersensitivity (DTH), its absence is often clinically overlooked. This study investigates the correlation between the lack of BCG scarring, immunological anergy, and fatal disseminated disease outcomes. **Case presentation:** We report a clinical-pathological analysis of two pediatric patients admitted to a tertiary care center in Indonesia. Case 1, an 11-month-old male vaccinated at birth, presented with status epilepticus and was diagnosed with Probable TBM Stage III. Despite vaccination, he lacked a BCG scar and exhibited Tuberculin Skin Test (TST) anergy (0 mm). Case 2, a 2-year-8-month-old female vaccinated at birth, presented with Type 1 respiratory failure due to severe miliary TB. She demonstrated profound wasting and TST anergy (0 mm). Both patients succumbed to the disease (Day 9 and Day 14, respectively) despite aggressive management. **Conclusion:** The absence of a BCG scar in vaccinated children serves as a critical clinical indicator of "immunological silence." It correlates with a failure to mount the Th1-mediated granulomatous response necessary for containing lymphohematogenous spread. We recommend that scar failure be treated as a risk factor requiring enhanced surveillance and a lower threshold for preventative therapy.

1. Introduction

Global and regional dynamics of tuberculosis (TB) remain a catastrophic global health challenge, an ancient scourge that has co-evolved with humanity for millennia, yet refuses to be relegated to history.[1] Despite the technological triumphs of modern medicine, TB continues to assert itself as the leading infectious killer worldwide, reclaiming its grim supremacy by surpassing HIV/AIDS in mortality statistics. It is a pandemic that moves in slow motion, often overshadowed by acute viral outbreaks, yet its toll is relentless. The burden of this disease is not distributed equally; it is disproportionately borne by the most vulnerable, particularly pediatric populations in endemic regions of the Global South. Southeast Asia, with its dense populations and pockets of resource-limited healthcare, stands at the epicenter of this crisis.[2]

Indonesia, currently ranking second globally in TB incidence, faces a unique and persistent challenge in pediatric TB management.[3] Here, the disease does not merely represent a pulmonary infection but a systemic threat. The defining tragedy of pediatric tuberculosis in this region is the "silent" progression from primary

infection to disseminated disease. Unlike immunocompetent adults, whose mature immune architectures are generally capable of walling off *Mycobacterium tuberculosis* within the pulmonary parenchyma—forming the classic Ghon complex—infants and young children possess a naive and developing immune system. This immunological immaturity creates a perilous "window of vulnerability." In these young hosts, the alveolar macrophages, the first line of defense, are often unable to contain the initial bacillary assault. Consequently, the pathogen bypasses local containment, eroding into the lymphatic and circulatory systems.

This rapid lymphohematogenous dissemination leads to severe, life-threatening phenotypes such as miliary tuberculosis and tuberculous meningitis (TBM).[4] Miliary TB, characterized by the "millet seed" dissemination of granulomas across multiple organs, and TBM, the invasion of the subarachnoid space by bacilli, represent the absolute failure of the host's immune surveillance. These disseminated forms are associated with devastating morbidity and mortality rates exceeding 20% to 50%, even when optimal pharmaceutical treatment is administered. For the survivors, the sequelae—ranging from severe neurological deficits to chronic pulmonary insufficiency—often mandate a lifetime of disability. The true tragedy of pediatric TB, however, lies not merely in its incidence or its lethality, but in its preventability. We possess the tools to prime the immune system against this invasion, yet in too many children, this priming fails.

BCG mechanism and immunological expectations for over a century, the Bacillus Calmette-Guérin (BCG) vaccine has stood as the sole immunizing agent available against tuberculosis.[5] First administered in 1921, this live attenuated strain of *Mycobacterium bovis* remains the cornerstone of pediatric TB prevention strategies globally. Its longevity in the immunization schedule is a testament to its specific utility: while it provides variable protection against adult pulmonary disease, its efficacy in preventing severe disseminated forms of TB in infants is well-established, estimated at 70% to 80%.

Understanding the failure of protection requires a granular understanding of the vaccine's intended mechanism. BCG relies fundamentally on the induction of a robust T-helper 1 (Th1) cell-mediated immune response. The vaccine acts as a "live drill" for the infant's immune system. Upon intradermal injection, the live attenuated bacilli are phagocytosed by professional antigen-presenting cells (APCs), specifically dermal dendritic cells and resident macrophages. These APCs process the mycobacterial antigens and migrate to the draining lymph nodes, where they present these molecular signatures to naive CD4+ T-cells via Major Histocompatibility Complex (MHC) Class II molecules.[6]

This interaction is the critical pivot point of immunity. In a successful vaccination event, the APCs secrete Interleukin-12 (IL-12), a cytokine that drives the differentiation of naive T-cells into Th1 effectors. These effector cells, in turn, unleash a cascade of pro-inflammatory cytokines, most notably Interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). IFN-γ is the potent activator of macrophages, enhancing their microbicidal capacity and enabling the formation of granulomas—organized structures of immune cells that physically sequester and destroy mycobacteria. Without this Th1 axis, the macrophage remains a permissive host, allowing the bacteria to replicate unchecked.[7]

Signifying "The Take" Clinically, this potent, localized inflammatory response at the injection site follows a predictable and visible evolution: the formation of a papule, followed by necrosis, ulceration, and eventual cicatrization. The result is the hallmark BCG scar. For decades, the formation of this scar has been viewed by epidemiologists and clinicians not as a cosmetic sequela, but as a vital surrogate marker for "vaccine take" and the successful induction of delayed-type hypersensitivity (DTH).

The scar is effectively a biological receipt of a successful skirmish between the host and the attenuated pathogen. Its presence signifies that the host possesses the cellular machinery to recognize,

attack, and wall off mycobacterial antigens. Scientific literature corroborates this clinical observation. Studies utilizing ex vivo cytokine assays have consistently demonstrated that infants who develop a scar generate significantly higher concentrations of IFN-γ and TNF-α in response to mycobacterial stimulation compared to those who remain scarless. The scar is a physical manifestation of high-magnitude cellular immunity.[8]

Furthermore, recent advances in immunology have illuminated a secondary benefit of the BCG vaccine known as "trained immunity." This phenomenon involves the epigenetic reprogramming of innate immune cells (monocytes and Natural Killer cells), enhancing their responsiveness not only to tuberculosis but to unrelated pathogens. Evidence suggests that the presence of a BCG scar is associated with a reduction in all-cause mortality in infants, likely due to this heterologous protection against respiratory infections and sepsis. Therefore, the scar represents a dual layer of protection: specific memory against TB and non-specific vigilance against other threats.

Despite the profound biological significance of the BCG scar, a critical gap exists in current clinical practice and public health policy—a gap through which children are slipping unnoticed. In Indonesia, the BCG vaccine is mandatory and administered shortly after birth, typically utilizing the Bio Farma strain (derived from the Pasteur strain 1173 P2).[9] This specific strain is historically known for its high reactogenicity and immunogenicity compared to less reactogenic strains like BCG Glaxo or Tokyo. Given the potency of the strain used, the expectation of scarring should be high.

However, a dangerous disconnect exists between administrative data and biological reality. While national programs report high administrative coverage rates—meaning the vaccine was injected—the biological success of these vaccinations is rarely audited. In the bustling environment of primary care and routine follow-ups, the presence of the scar is seldom documented with the same rigor as the date of injection. Current national guidelines and World Health Organization (WHO) protocols do not mandate revaccination for scar-negative children, nor do they formally classify scar absence as a specific risk factor for severe disease.

This passive approach fosters an illusion of safety. It assumes that "vaccinated on paper" equates to "protected in vivo." This assumption is clinically dangerous. The phenomenon of "vaccine failure" in BCG is complex and multifactorial. It may stem from technical issues, such as cold-chain incompetence (rendering the live bacteria non-viable before injection) or administration errors (such as subcutaneous rather than intradermal injection, which fails to recruit dermal dendritic cells). Alternatively, and perhaps more ominously, scar failure may reflect host-specific vulnerabilities. These can range from severe nutritional deficiencies that suppress immune responsiveness to subtle genetic susceptibility traits, such as Mendelian Susceptibility to Mycobacterial Disease (MSMD), where mutations in the IFN-γ/IL-12 pathway render the child incapable of mounting a granulomatous response. When a vaccinated child fails to scar, it is not merely a failure of dermatology; it may signal a profound immunological anergy. It suggests an intrinsic inability of the host to generate the very response necessary to wall off a mycobacterial invader. By ignoring the absence of a scar, we may be missing the first and only warning sign that a child is immunologically defenseless against the world's leading infectious killer.[10]

This paper aims to bridge the widening chasm between immunological theory and the stark realities of clinical practice in high-burden settings. While statistical analyses of vaccine efficacy abound, there is a paucity of detailed clinical-pathological correlations that examine the specific fate of the "scarless" vaccinated child. We present a rigorous analysis of two fatal cases of disseminated tuberculosis—Miliary TB and Tuberculous Meningitis—in children who received timely BCG vaccination but failed to develop the characteristic scar. By integrating detailed clinical timelines,

radiographic evidence, and a deep-dive pathophysiological analysis, we challenge the current clinical indifference toward scar failure. This study is novel in its framing of the absent scar not as a neutral variable, but as a prodromal indicator of fatal susceptibility. We hypothesize that the absence of a BCG scar acts as a visible "red flag" for immunological silence, correlating with a failure of the Th1 immune axis that leaves the pediatric host vulnerable to rapid, unchecked, and fatal dissemination. Through these cases, we advocate for a paradigm shift: treating the scarless child as a high-risk patient requiring enhanced surveillance, distinct from their scarred peers.

2. Case Presentation

Case 1: Fatal tuberculous meningoencephalitis

Patient profile and history

The tragedy of disseminated pediatric tuberculosis often arrives in the emergency room disguised as an acute neurological catastrophe. Such was the case with Patient A, an 11-month-old male infant who was urgently admitted to the Pediatric Intensive Care Unit (PICU) of a tertiary referral hospital in Indonesia. The clinical tableau upon arrival was dire: the infant was in status epilepticus, a state of unremitting seizure activity that had already compromised his airway and hemodynamic stability.

The mother provided a harrowing history of the preceding 72 hours, describing a rapid neurological descent characterized by recurrent generalized tonic-clonic seizures and a progressive decline in consciousness, culminating in his current comatose state. However, a meticulous reconstruction of the history revealed that this "acute" event was merely the terminal chapter of a much longer, silent siege. The history of present illness unveiled a three-week prodrome that had been tragically misinterpreted. The infant had suffered from high-grade, intermittent fevers—classic for the release of pyrogens from a high bacillary load—accompanied by marked irritability. In retrospect, this irritability was likely the earliest clinical sign of meningeal irritation (meningism), a cry for help from an inflamed central nervous system. Concurrently, he developed stomatitis and a persistent, non-productive cough lasting one month. This cough was not a benign viral remnant; it was the audible signal of the primary pulmonary focus, the initial beachhead from which the mycobacteria launched their systemic invasion. Three days prior to admission, the invasion breached critical neurological thresholds, manifesting as focal neurological deficits: rightward eye deviation and limb rigidity, signaling irritation of the motor cortex and increasing intracranial pressure.

The epidemiological investigation of Case 1 exposes a dual failure of the public health safety net: the failure of primary immunization and the failure of contact prophylaxis. Kartu Menuju Sehat (Maternal and Child Health Handbook) provided documentary proof that BCG vaccination was administered at one month of age at a primary health center. On paper, this child was "protected." However, physical verification told a different story. Inspection by two independent pediatricians revealed no evidence of a BCG scar over either deltoid region. This discordance between the administrative record and the biological phenotype is the crux of this case. The absence of the scar suggests that despite the injection, the child's immune system remained "immunologically silent," failing to mount the Th1 response necessary for memory formation. The source of the infection was domestic and distinct. The patient's father was in the fifth month of treatment for smear-positive pulmonary tuberculosis. This placed the infant in the highest risk category imaginable: a household contact of an active shedder. Crucially, despite the known paternal infection, the infant had received no preventative isoniazid prophylaxis. This represents a catastrophic failure in the contact tracing system. Had the child been started on prophylaxis when the father was diagnosed, the progression from primary infection to lethal dissemination might have been halted. Instead, the "scarless" and unprotected infant was left fully exposed to a massive daily inoculum of M. tuberculosis.

Upon admission, the clinical examination revealed a child in the throes of advanced neurological failure. The patient was profoundly comatose with a Glasgow Coma Scale (GCS) of 4 (E1V2M1), a level of unconsciousness bordering on brain death. The pupils were anisocoric (3mm vs. 5mm) with a sluggish light reflex, a grave sign of uncal herniation compressing the oculomotor nerve. Noxious stimulation elicited decerebrate posturing—rigid extension of the arms and legs—indicating that the damage had extended deep into the brainstem. The infant was hemodynamically unstable, exhibiting tachycardia (178 bpm) and tachypnea (58 bpm), with a fever of 39.2°C. These signs reflected not just infection, but a central autonomic storm driven by rising intracranial pressure (ICP). The physical manifestations of raised ICP were unmistakable. The anterior fontanelle was tense, bulging, and non-pulsatile. Nuchal rigidity and opisthotonus (severe arching of the back) confirmed profound irritation of the meninges. Choreoathetoid movements suggested the infection had ravaged the basal ganglia, a common site for vascular complications in TBM. Weighing only 6.2 kg (Weight-for-Age Z-score <-3 SD), the infant was severely malnourished. This marasmic state was likely synergistic: the chronic infection drove catabolism, while the malnutrition further dismantled the cellular immune response, creating a vicious cycle of susceptibility.

The Anteroposterior Chest X-ray was diagnostic of hematogenous dissemination. It revealed a diffuse reticulonodular pattern distributed evenly throughout both lung fields. This "snowstorm" appearance is pathognomonic for Miliary TB, representing thousands of granulomas formed where bacilli settled from the bloodstream. It confirmed that the containment failure was systemic, not just neurological. The lumbar puncture confirmed the diagnosis of TBM. The opening pressure was elevated at 28 cmH_2O, reflecting acute hydrocephalus. The fluid was xanthochromic (yellow-tinged), indicating high protein content and older hemorrhage from vasculitis. The cell count showed pleocytosis (350 cells/μL) with a lymphocytic predominance (85%), the hallmark of tubercular meningitis. The protein was markedly elevated at 250 mg/dL (indicating disruption of the blood-brain barrier and spinal block), while glucose was critically low at 15 mg/dL (ratio <0.2), confirming bacterial consumption. Despite this overwhelming burden of disease, the Tuberculin Skin Test (TST) resulted in an induration of 0 mm (Anergic). This result is pivotal. It signifies that the child's T-cells were either completely depleted by the overwhelming sepsis (secondary anergy) or, more likely given the scar failure, were never primed in the first place (primary anergy).

The patient was diagnosed with Probable Tuberculous Meningitis Stage III and Miliary Tuberculosis, with a Pediatric TB Score >6. Management was aggressive and adhered to international standards for severe TBM. A high-dose, four-drug regimen was initiated immediately: Isoniazid (10 mg/kg), Rifampicin (15 mg/kg), Pyrazinamide (35 mg/kg), and Ethambutol (20 mg/kg). High-dose Dexamethasone (0.4 mg/kg/day) was administered to dampen the "cytokine storm" within the subarachnoid space, aiming to prevent the adhesive arachnoiditis that leads to hydrocephalus and stroke. Mannitol and hypertonic saline were used to combat cerebral edema. Seizures were managed with Phenytoin loading. Despite this maximalist approach, the disease course was irreversible. The pathology of Stage III TBM—involving vasculitic infarction, brainstem compression, and hydrocephalus—had advanced beyond the reach of pharmacology. The patient developed the ominous signs of Cushing's triad and autonomic instability, markers of terminal brainstem herniation. He succumbed to cardio-respiratory arrest on hospitalization day 9. This case serves as a grim autopsy of a "vaccinated" child who possessed no immunity, highlighting that in the absence of a scar and prophylaxis, the BCG record offered no protection against the lethal dissemination of the father's disease.

Case 2: Miliary tuberculosis with respiratory failure

While Case 1 illustrated the failure of the blood-brain barrier, Case 2 demonstrates the catastrophic collapse of pulmonary integrity. The patient, a 2-year-8-month-old female, presented to the emergency department not with seizures, but with "air hunger"—severe dyspnea and central cyanosis that marked the terminal phase of chronic respiratory failure. The maternal history revealed a slow, insidious progression that had been masked by the non-specific nature of the symptoms. For two weeks, the child had exhibited progressive breathlessness, initially only with exertion but advancing to dyspnea at rest. This respiratory distress was preceded by a three-week prodrome of low-grade fever and a productive cough, symptoms easily dismissed in a tropical setting as a common viral illness. However, the most alarming feature was the "silent wasting." The mother reported significant weight loss of 2 kg in the preceding month—approximately 20% of the child's total body weight. This rapid cachexia was not merely nutritional; it was metabolic, driven by the intense caloric demands of a systemic infection and the chronic work of breathing.

The epidemiological review of Case 2 presents a compelling timeline that challenges the conventional understanding of malnutrition-induced immune suppression. Immunization records confirmed that the BCG vaccine was administered at birth, adhering to the national schedule. Clinical examination, however, confirmed the complete absence of a BCG scar. A crucial aspect of this case is the chronological relationship between the failure to scar and the onset of malnutrition. The child was born at a normal birth weight and maintained a normal growth curve for the first year of life. Growth faltering was only noted starting at 12 months of age. Since the BCG scar typically matures within 12 weeks (3 months) of vaccination, the scar failure occurred nearly 9 months before the onset of malnutrition. This timeline strongly suggests that the failure to scar was a primary immunological event—a failure of the vaccine to take in a healthy host—rather than a secondary consequence of nutritional deficiency. The child entered her second year of life with a false sense of protection, "vaccinated" but biologically naive to mycobacteria.

At presentation, the child was in frank respiratory failure, fighting for every breath. The respiratory rate was tachypneic at 64 breaths/minute. The work of breathing was immense, evidenced by marked subcostal, intercostal, and suprasternal retractions. Oxygen saturation was critically low at 85% on room air, indicating a severe ventilation-perfusion mismatch. Auscultation revealed the terrifying sound of "Velcro crackles"—diffuse, coarse crepitations heard bilaterally across all lung fields. This sound represents the snapping open of fluid-filled alveoli and stiffened interstitium, characteristic of widespread fibrotic or granulomatous lung disease. The physical toll of the disease was visible. With a weight of 8.5 kg and height of 82 cm, her Weight-for-Height Z-score was <-3 SD, confirming severe acute malnutrition (SAM). She appeared "skin and bones," with loss of buccal fat pads and muscle atrophy, hallmarks of the "consumptive" nature of untreated tuberculosis. Physical examination also revealed extensive oral thrush and intertriginous candidiasis. In the absence of HIV (which was tested and negative), these opportunistic fungal infections served as a clinical marker for severe T-cell dysfunction. The disseminated TB had likely exhausted the cellular immune system, leaving the mucocutaneous barriers undefended.

The Chest X-ray offered a stark visualization of the pathology. It displayed diffuse, uniform, millet-seed-sized opacities (<2mm) distributed throughout both lung fields. In the lower zones, these nodules had begun to coalesce, creating areas of consolidation. This "white-out" appearance is consistent with severe Miliary TB complicated by acute respiratory distress syndrome (ARDS). The lung parenchyma, replaced by granulomas and inflammatory exudate, had lost its compliance, becoming stiff and unable to facilitate gas exchange. The complete blood count revealed a

hypochromic microcytic anemia (Hemoglobin 8.2 g/dL), likely anemia of chronic inflammation. More critically, there was Severe Lymphopenia (Absolute Lymphocyte Count < 1,500/μL). In the context of miliary TB, this lymphopenia is often a result of sequestration; lymphocytes are recruited out of the blood and into the millions of granulomas in the lungs, liver, and spleen, leaving the peripheral circulation depleted. The arterial blood gas (ABG) painted a picture of uncompensated failure: pH 7.25 (Acidosis), pCO_2 55 mmHg (Hypercapnia/Ventilatory Failure), and pO_2 55 mmHg (Severe Hypoxemia). The child was retaining carbon dioxide because her fatigued respiratory muscles could no longer pump air in and out of her stiff lungs. Sputum GeneXpert MTB/RIF was negative. This is a common and frustrating reality in pediatric miliary TB. The disease is often paucibacillary (low bacterial load in secretions) because the granulomas are interstitial (in the tissue) rather than endobronchial (in the airways). The negative test did not rule out the disease; the clinical and radiographic evidence was overwhelming. Like Case 1, the TST revealed an induration of 0 mm (Anergic), confirming the complete absence of a peripheral DTH response.

The patient was diagnosed with Severe Miliary Tuberculosis with Type 1 Respiratory Failure and Severe Acute Malnutrition. She was immediately intubated and placed on mechanical ventilation. The management of miliary TB-induced ARDS is notoriously difficult. The stiff, granuloma-filled lungs require high pressures to open, yet are susceptible to barotrauma. Ventilator settings were optimized for low compliance (High PEEP of 8 cmH_2O to recruit alveoli, FiO_2 100%), but oxygenation remained refractory. A 4-drug anti-TB regimen (RHZE) was administered via nasogastric tube. Nutritional rehabilitation was initiated cautiously with the F-75 therapeutic formula to avoid refeeding syndrome, a potentially fatal electrolyte shift in starved patients. Despite establishing an artificial airway and delivering maximal medical therapy, the damage to the alveolar-capillary membrane was irreversible. The patient developed Multi-Organ Dysfunction Syndrome (MODS) as the hypoxia led to myocardial depression and renal injury. The clinical course was a slow, agonizing slide into metabolic silence. She died on hospital day 14, succumbing to refractory hypoxemia and cardiac arrest. Her case underscores that in the absence of the "biological shield" of a successful BCG response, miliary TB acts as a systemic malignancy, destroying lung tissue faster than antibiotics can heal it.

3. Discussion

The two cases presented herein illustrate a devastating, almost algorithmic trajectory of tuberculosis in early childhood: prior vaccination, absence of scarring, failure of local containment, hematogenous dissemination, and death. These are not merely case reports of treatment failure; they are autopsies of prevention failure. While pediatric TB mortality is often multifactorial—a complex interplay of exposure intensity, nutritional status, and healthcare access—the specific phenotype of the "vaccinated but scar-negative" child warrants a detailed pathophysiological examination. This phenotype represents a distinct clinical entity, one that challenges the binary assumption that a child is either "vaccinated" or "unvaccinated." Instead, it exposes a grey zone of "immunological silence," where the administrative act of vaccination has occurred, but the biological event of immunization has failed. To understand why these children died, we must first understand what failed to happen in their skin months earlier. The formation of a BCG scar is frequently dismissed as a cosmetic sequela, a mere mark of coverage. In reality, it is the physical manifestation of a successful, robust, and localized T-cell mediated immune response. It is a biological receipt of engagement.[11]

Upon intradermal injection, the live attenuated *Mycobacterium bovis* bacilli are intended to act as a provocative agent. They are phagocytosed by dermal dendritic cells and resident macrophages, the sentinels of the innate immune system (Figure

1).[12] In an immunocompetent "responder," these antigen-presenting cells (APCs) migrate to the regional lymph nodes, processing the mycobacterial antigens and presenting them to naive CD4+ T-cells via Major Histocompatibility Complex (MHC) Class II molecules. This interaction triggers the release of a specific cytokine milieu, dominated by Interleukin-12 (IL-12), which drives the differentiation of naive T-cells into Th1 effectors. These Th1 effectors then return to the injection site, unleashing a potent local inflammatory cascade characterized by the release of Interferon-gamma (IFN-γ) and Tumor Necrosis Factor-alpha (TNF-α). This cytokine storm activates macrophages, transforming them into epithelioid cells that aggregate to form a granuloma—a fortress built to contain the bacilli. The necrosis, ulceration, and subsequent cicatrization (scarring) that follow are visible byproducts of this fierce microscopic battle.[13]

Table 1. Comparative Clinical-Pathological Profile

Fatal Disseminated Tuberculosis in Vaccinated Children with Failed BCG Scar Formation

PARAMETER	CASE 1 (NEUROLOGICAL)	CASE 2 (RESPIRATORY)
Patient Profile	11-month-old Male Admitted to PICU	2-year-8-month-old Female Emergency Presentation
Final Diagnosis	Fatal **Probable TBM Stage III + Miliary TB** *Pediatric TB Score > 6*	Fatal **Miliary TB + Type 1 Respiratory Failure** *Complicated by MODS*
BCG Vaccination & Scar	HISTORY: Verified (at 1 month) SCAR: **ABSENT**	HISTORY: Verified (at birth) SCAR: **ABSENT**
Immunological Status	TST: 0 mm (Anergic) HIV Non-reactive	TST: 0 mm (Anergic) Severe Lymphopenia (<1500/µL) Extensive Candidiasis
Nutritional Status	Severe Malnutrition Weight-for-Age Z-score < -3 SD	Severe Wasting (Marasmus) Weight-for-Height Z-score < -3 SD 20% weight loss in 1 month
Clinical Presentation	• Status Epilepticus • Coma (GCS 4) • Decerebrate Posturing • Bulging Fontanelle	• Severe Dyspnea ("Air Hunger") • Central Cyanosis • "Velcro Crackles" • Severe Retractions
Radiology (CXR)	Diffuse "Snowstorm" Appearance Even distribution of fine nodules	"White-out" Lung Fields Coalescent nodules & consolidation Consistent with ARDS
Key Investigations	**CSF Analysis:** • High Opening Pressure (28 cmH2O) • Xanthochromia • Pleocytosis (350 cells/µL) • High Protein / Low Glucose	**Blood Gas Analysis:** • Uncompensated Resp. Acidosis • pH 7.25 • Severe Hypoxemia (pO2 55 mmHg) • Hypercapnia (pCO2 55 mmHg)
Outcome	**Death (Day 9)** Due to Brainstem Herniation	**Death (Day 14)** Due to Refractory Hypoxemia/MODS

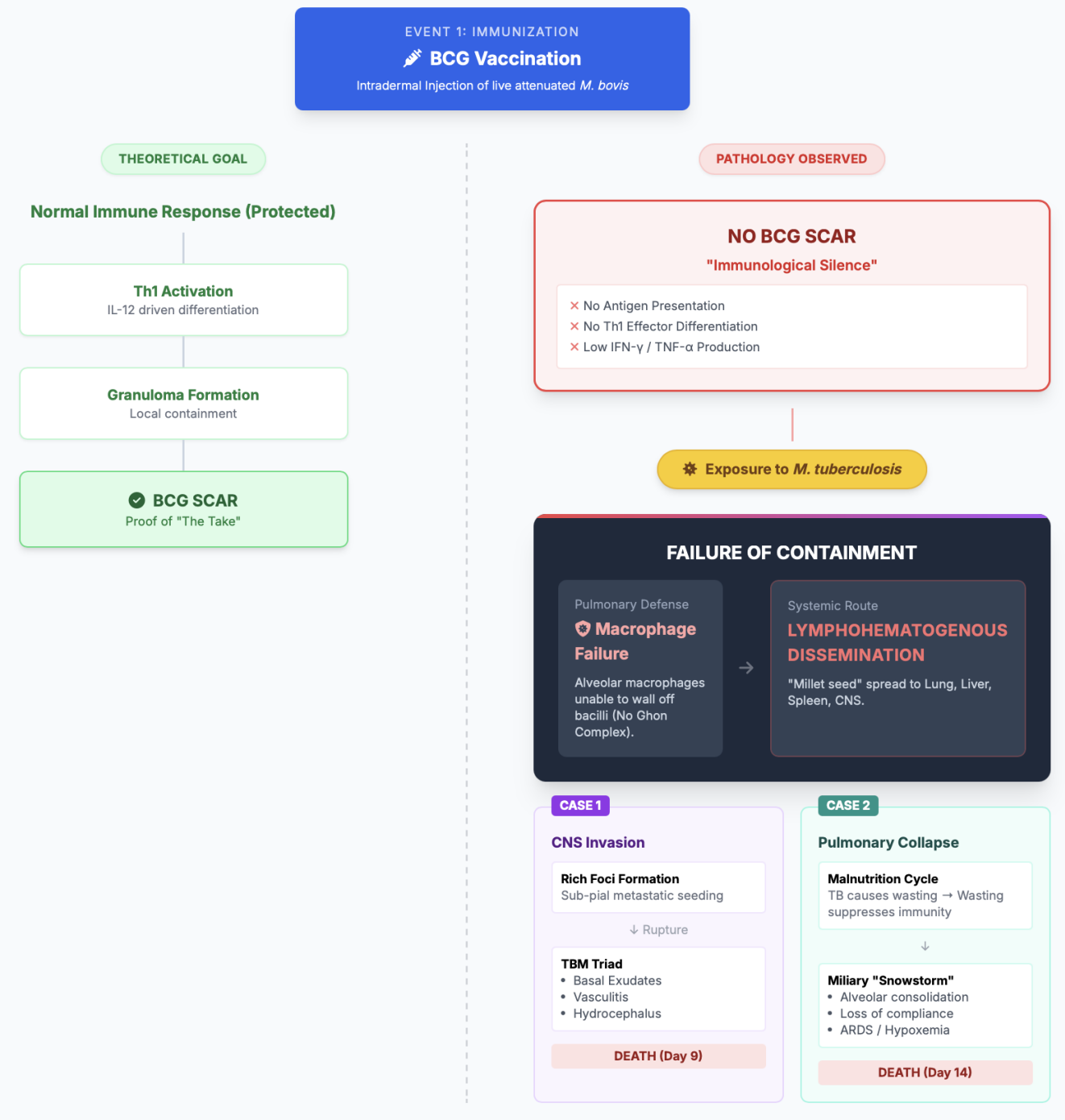

Figure 1. Algorithmic trajectory of fatal dissemination.

In our two cases, the absence of the scar serves as clinical evidence that this specific immunological axis was disrupted. The "silence" at the injection site implies that the initial interaction between the vaccine strain and the host immune system was abortive. Studies utilizing ex vivo cytokine assays have consistently demonstrated that infants who do not scar generate significantly lower concentrations of IFN-γ upon stimulation with mycobacterial antigens. By failing to scar, these children signaled a pre-

existing state of "immunological silence." They failed to recognize the attenuated vaccine strain, which translated directly into a fatal inability to recognize and contain the virulent *M. tuberculosis* strain when it invaded months later.[14]

A critical methodological and clinical distinction must be addressed regarding the negative Tuberculin Skin Test (TST) results (0 mm) observed in both cases. In clinical parlance, this is termed "anergy"—the absence of a delayed-type hypersensitivity (DTH) reaction. However, the origin of this anergy is not uniform, and distinguishing its cause is vital for understanding the pathogenesis.

It is well-established in TB pathology that overwhelming disseminated disease can cause secondary anergy. In states of massive bacterial load, such as Miliary TB, the peripheral circulation is depleted of antigen-specific T-lymphocytes. These cells are not absent from the body; rather, they are sequestered, recruited out of the blood and into the millions of granulomas seeding the lungs, liver, and spleen.[15] This "sequestration effect" likely explains the profound lymphopenia observed in Case 2 and contributes to the negative TST in the acute phase. The immune system is not silent; it is overwhelmed and fully deployed elsewhere.

However, we argue that Primary Anergy—a fundamental failure of vaccine uptake—was the precipitating event in these cases. The evidence lies in the historical timeline. The BCG scar failed to form months to years before the acute TB infection occurred. This historical lack of response indicates that the children never mounted the initial Th1 response required for memory T-cell formation. The "anergy" did not begin when the child became sick; it began when the child was vaccinated. Thus, the negative TST observed on admission was not merely a result of the disease (exhaustion), but a confirmation of the host's long-standing, intrinsic immunological unresponsiveness to mycobacterial antigens (naivety). These children were biologically "virgin" hosts to the tubercle bacillus, despite their vaccination records.

The progression of Case 1 to fatal tuberculous meningitis (TBM) provides a grim illustration of what happens when the "biological shield" of cellular immunity is absent. The BCG vaccine is historically credited with 70-80% efficacy against TBM not because it prevents infection, but because it prevents dissemination. It primes the immune system to contain bacilli within the primary lymph node complex (the Ghon complex) in the lungs. In Case 1, this containment failed completely. Without a primed Th1 response to activate macrophages, the bacilli were not walled off in the lungs.[16] Instead, they eroded into the bloodstream—a massive lymphohematogenous dissemination. These circulating bacilli then seeded the central nervous system, crossing the Blood-Brain Barrier (BBB) to establish sub-pial or sub-ependymal metastatic foci, known as "Rich foci."

In an immunocompetent, scarred child, these foci might have been contained. But in this "scarless" infant, the foci grew unchecked until they ruptured into the subarachnoid space. This rupture released a bolus of mycobacterial antigens into the cerebrospinal fluid (CSF), triggering a catastrophic, albeit delayed, hypersensitivity reaction. This resulted in the classic and lethal triad of TBM pathology: (1) Basal Exudates**:** A thick, gelatinous inflammatory exudate coated the base of the brain, strangulating the cranial nerves and cerebral vessels; (2) Vasculitis: The inflammation attacked the vessels of the Circle of Willis, leading to potential infarctions (strokes) that further devastated the brain parenchyma; (3) Hydrocephalus: The exudate blocked the reabsorption of CSF, leading to the dangerously elevated intracranial pressure that caused the child's coma and eventual brainstem herniation. The rapid death (9 days) underscores that without the cellular immunity evidenced by scarring, the BBB is defenseless. The vaccine is the sentry; without it, the fortress falls.

Malnutrition acts as a significant confounder in pediatric TB, particularly evident in Case 2. The relationship between malnutrition and tuberculosis is bidirectional and synergistic—a "vicious cycle" where each exacerbates the other. Severe wasting leads to

thymic atrophy, reducing the output of naive T-cells, and impairs the functional capacity of cytokines, effectively causing a state of acquired immunodeficiency (nutritional AIDS).[17] A skeptic might argue that malnutrition was the cause of the vaccine failure in Case 2. However, the chronology serves as a critical counter-argument. The child was vaccinated at birth with a normal birth weight and grew well for the first year. The scar typically matures within 3 months of vaccination. The growth faltering (malnutrition) did not begin until 12 months of age. Therefore, it is biologically plausible, if not probable, that the failure to scar was an independent immunological event (primary vaccine failure) that occurred in a well-nourished host. This failure left the child vulnerable. Subsequently, when the child was exposed to TB, the primary infection progressed to disease, inducing a hyper-catabolic state that drove the child into severe malnutrition (secondary wasting). This wasting then further suppressed the immune system, accelerating the terminal decline. The malnutrition was likely the fuel, but the scar failure was the spark.[18]

In analyzing cases where vaccination fails so profoundly in the absence of HIV, we must consider the host's genetic architecture. Specifically, we must consider Mendelian Susceptibility to Mycobacterial Disease (MSMD)**.** This group of rare, inborn errors of immunity involves specific mutations in the IL-12/IFN-γ pathway—genes such as IFNGR1, IFNGR2, IL12RB1, and *STAT1*. Children with MSMD have a specific "hole" in their immune repertoire: they are selectively vulnerable to intracellular mycobacteria. They may fail to respond to the attenuated BCG vaccine (resulting in no scar and no protection) or, conversely, they may be overwhelmed by it, developing disseminated BCG-osis. When exposed to *M. tuberculosis*, they are unable to form granulomas, leading to rapid, fulminant dissemination. While genetic sequencing was not available in this resource-limited setting, the clinical triad observed—"No Scar + Disseminated TB + Fatal Outcome"—is highly suggestive of an underlying immunogenetic defect. These children represent a "canary in the coal mine." Future research in Indonesia should prioritize genetic screening for such "scar-negative" casualties to understand the prevalence of these silent genetic vulnerabilities in the population.[19]

The tragedy of these two cases extends beyond the biological to the systemic. Current national guidelines in Indonesia, aligned with many high-burden countries, do not mandate routine verification of the BCG scar. The immunization record is considered proof enough. These cases challenge that passivity. If the absence of a scar is a proxy for poor immune priming—a visible marker of "vaccine failure"—then these children represent a distinct, high-risk subgroup. They are effectively unvaccinated in a sea of tuberculosis. We propose a shift in public health protocol: (1) Clinical Audit: BCG scar assessment at 3 months of age (concurrent with DPT vaccination) should be integrated into the national immunization program; (2) Risk Stratification: Infants without scars, especially those with household TB contacts (like Case 1), should be red-flagged. They should be prioritized for repeat TST screening and, crucially, should have a lower threshold for initiating preventative chemoprophylaxis; (3) Revaccination Debate: While WHO currently does not recommend revaccination due to lack of evidence for efficacy, this policy is based on population-level data. For the individual child with "no take," the debate must be reopened. We must replace the false sense of security provided by the "paper" immunization record with the clinical verification of the "biological" record. In a country where TB is the second leading killer, a vaccinated child without a scar should be treated with the same index of suspicion and protective urgency as a child who was never vaccinated at all.[20]

4. Conclusion

This case series provides compelling clinical and pathological evidence that a documented history of BCG vaccination does not guarantee protection against fatal dissemination, particularly when the

characteristic scar is absent. The lack of scarring serves as a visible historical record of immunological anergy—a failure to mount the Th1 response necessary for containment. Whether due to technical administration failure, nutritional suppression, or genetic susceptibility (MSMD), the "scar-negative" child is biologically vulnerable. We strongly advocate for the elevation of BCG scar assessment from a casual observation to a critical clinical indicator. In high-burden settings like Indonesia, a vaccinated child without a scar should be treated with the same index of suspicion as an unvaccinated child.

5. References

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