SYSTEMATIC REVIEW

Assessing Safety and Immunogenicity in Development of Aerosolized Tuberculosis Vaccine Versus Injected Vaccine: Systematic Review of Randomized Controlled Trial Studies

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ABSTRACT

Introduction: Tuberculosis (TB) remains the second leading cause of death from infectious diseases worldwide. The Bacillus Calmette-Guerin (BCG) vaccine exhibits limitations in efficacy and potential complications associated with its administration. To address these limitations, aerosolized TB vaccines are being developed. This study evaluates safety and immunogenicity of aerosol administration of TB vaccination. **Methods:** This systematic review was conducted following PRISMA guidelines. Inclusion criteria encompassed healthy human randomized trials, comparing aerosol-delivered TB vaccines to those administered via injection, with a focus on safety and immunogenicity outcomes. **Results:** Four studies indicate that aerosolized vaccines significantly ($p<0.05$) enhanced immune response in respiratory mucosa and blood, as evidenced by increased levels of cytokines, including TNFα, IFNγ, IL-2, and IL-17, in response to Ag85A-specific, MVA-specific, and total cytokines. There was no significant difference in the number of adverse events between injected and aerosol groups ($p>0.05$). **Conclusion:** Aerosolized tuberculosis vaccines demonstrate significant potential for eliciting immune responses and are regarded as safe.
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Keywords: aerosol, tuberculosis, BCG vaccine, immunogenicity, vaccine safety

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INTRODUCTION

According to World Health Organization (WHO) data, in 2025, there were about 10.7 million cases of Tuberculosis (TB) with approximately 1.23 million deaths. This puts TB as the 13th most deadly disease and second as the most lethal infectious disease after COVID-19 (1). The incidence of tuberculosis in Indonesia is also relatively high and Indonesia currently ranks third globally in TB incidence (2). The way to prevent TB that has been done until now is by administering the Bacillus Calmette-Guerin (BCG) vaccine, which is usually given during childhood. However, the present issue is that the BCG vaccine's effectiveness is only anticipated to last 10-20 years, depending on the type of exposure and how often exposed to TB. The efficacy and safety of the BCG vaccine can also be affected by various things, resulting in varying manifestations. It can also lead to multiple complications.

The most common complications of intradermal BCG vaccination are injection site reactions, ranging from granulomatous lesions, erythema, and radiating pain to lymphadenopathy (3,4). Other complications due to improper injection procedures, such as muscle tissue fibrosis, abscess, gangrene, neuropathy, periostitis, osteomyelitis, Human Immunodeficiency Virus (HIV) infection, viral hepatitis, and vascular injury can occur, so their use is highly dependent on the ability of medical professionals (5,6). Therefore, many new BCG vaccines, boosters, or replacements have been developed to increase immunity more safely and effectively (7).

One of the innovations being developed is the administration of tuberculosis vaccines intranasally or aerosolized. Considering that the main entrance of tuberculosis infection is through the respiratory tract, intranasal administration of the vaccine is expected to increase the body's immunity, especially in the airway mucosa. In addition, intranasal vaccine administration does not require professional personnel or medical equipment (8). Several primary studies have conducted intranasal vaccine trials in humans with a randomized controlled trial study design. However, there is still no

review study that specifically compiles these primary studies and assesses their overall immunogenicity and safety effects. Therefore, this review was made to review the immunogenicity and safety effects of aerosolized vaccines compared to injectable vaccines from existing primary studies.

METHODS

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol of this review was registered in PROSPERO with ID Number CRD42024606648.

Search strategies

Literature search was conducted on June 15, 2024, through seven databases, PubMed, Scopus, Sage, Cochrane library, Science direct, ProQuest and Google Scholar. All terms were aligned with Medical Subject Headings (MeSH) and all keywords are combined using the Boolean operator, resulting following keyword: ("Inhaler" OR "aerosol" OR "Intranasal" OR "Nebulizer") AND ("Immunisation" OR "Immunization" OR "Vaccine") AND ("Tuberculosis" OR "TB" OR "Mycobacterium") AND ("Randomized" OR "Randomised"). The details for each database keyword can be seen in Table I.

Study Selection

The search results from each database were collected collectively using Rayyan.ai. Then, duplicate detection was performed, followed by removal of duplicate articles. Screening was performed on the remaining articles based on title and abstract. All articles were then pooled for screening based on eligibility criteria. The purpose behind the exclusion of each article at each stage has been stated in the accompanying PRISMA flowchart (Figure 1). The entire literature search and study selection process were carried out by HNR, MFH, MSA, and HTS, with DA mediating any disagreements.

Eligibility Criteria

Study inclusion criteria are: (1) Study type, randomized trials; (2) Study population, humans; (3) Intervention, aerosolized TB vaccine; (4) Study outcome, including all measures of immunogenicity; (5) Comparison, intradermal/intramuscular injection TB vaccine group. Meanwhile, the exclusion criteria are as follows: (1) Protocol and review studies; (2) Studies that could not be accessed in full text; (3) Studies that were not published in English. No restriction was applied regarding publication date.

Data Extraction

The researcher extracted data from each study, which was preceded by data tabulation in a spreadsheet by MFH. The study data extraction was presented in tabular form by entering the following data: author and year of publication, sample size and group assignment, age range/mean, vaccine type, duration of intervention, study outcomes, and adverse events.

Table I: Search Strategy and Search Results by Database

Database	Keyword	Filter	Result
Scopus	("Inhaler" OR "aerosol" OR "Intranasal" OR "Nebulizer") AND ("Immunisation" OR "Immunization" OR "Vaccine") AND ("Tuberculosis" OR "TB" OR "Mycobacterium") AND ("Randomized" OR "Randomised")	-	16
Sage	("Inhaler" OR "aerosol" OR "Intranasal" OR "Nebulizer") AND ("Immunisation" OR "Immunization" OR "Vaccine") AND ("Tuberculosis" OR "TB" OR "Mycobacterium") AND ("Randomized" OR "Randomised")	research article only	14
Web of science	("Inhaler" OR "aerosol" OR "Intranasal" OR "Nebulizer") AND ("Immunisation" OR "Immunization" OR "Vaccine") AND ("Tuberculosis" OR "TB" OR "Mycobacterium") AND ("Randomized" OR "Randomised")	-	15
Google scholar	("Inhaler" OR "aerosol" OR "Intranasal" OR "Nebulizer") AND ("Immunisation" OR "Immunization" OR "Vaccine") AND ("Tuberculosis" OR "TB" OR "Mycobacterium") AND ("Randomized" OR "Randomised")	-	997
PubMed	#1 "Inhaler"(Title/Abstract) OR "aerosol"(Title/Abstract) OR "Intranasal"(Title/Abstract) #2 "Administration, Intranasal"(Mesh) #3 "Immunisation"(Title/Abstract) OR "Immunization"(Title/Abstract) #4 "Immunization"(Mesh) #5 "Tuberculosis"(Title/Abstract) OR "TB"(Title/Abstract) OR "Mycobacterium"(Title/Abstract) #6 "Tuberculosis"(Mesh) #7 #1 OR #2 #8 #3 OR #4 #9 #5 OR #6 #10 #7 AND #8 AND #9	-	5

Risk of Bias in Individual Studies (Qualitative synthesis)

Researchers evaluated the quality of each study using ROB 2.0. This tool evaluates five domains that refer to bias in randomization, bias owing to deviation from the intervention, bias resulting from missing outcome data, bias in outcome measures, and bias in outcome reporting. All authors assessed each inclusion study independently and wrote the results on a spreadsheet to be visualized using ROBVIS.

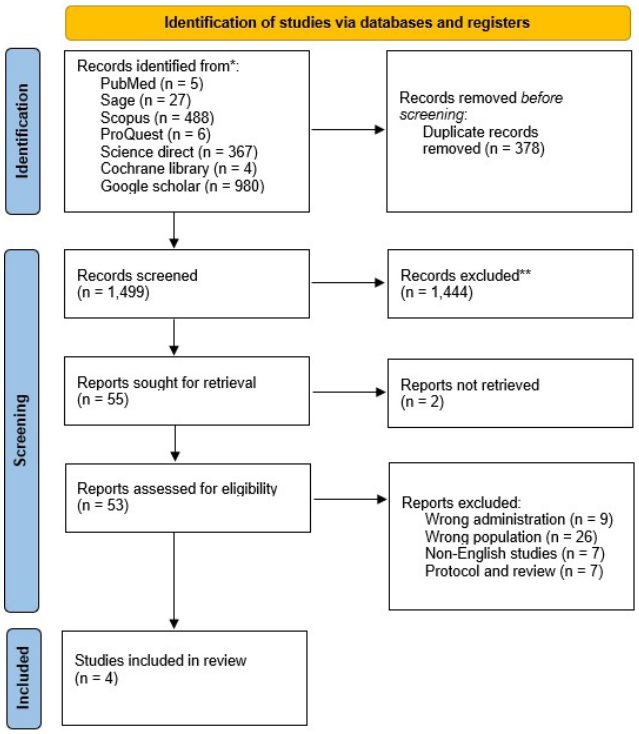

Figure 1: PRISMA Flow Diagram of Study Selection Process

RESULTS

Study Selection and Study Quality

After the search process in seven databases, 1,877 articles were collected. There were 378 duplicate articles removed, leaving 1,499 articles. There were 1,444 articles excluded, as they contained words or sentences that met the exclusion criteria. This left 55 articles for selection. All researchers (HNR, MFH, MSA, and HTS) conducted the screening process based on title and abstract, leaving 2 conflict articles to be read in full. Finally, 49 of the 53 articles were disqualified because they did not fulfil the inclusion criteria or fell into the exclusion criteria, leaving four articles for complete analysis. Two inclusion studies showed a low risk of bias after being analyzed using RoB 2.0 (9,10), while the other two showed some concerns because of issues over the possibility of bias in the 4th domain (3,11). Details for the risk of bias analysis results can be seen in (Figure 2).

Qualitative Synthesis Results

This review summarizes information from four inclusion studies from different countries: the United Kingdom (2 studies), Switzerland, and Canada. The total number of participants in these studies was 121 adults. The study duration of all inclusion studies was 24 weeks or 168 days. The types of vaccines and doses used varied, details of which can be seen in Table II. Overall, aerosolized vaccines significantly ($p<0.05$) increased the immune response in the respiratory mucosa when compared with baseline and with the injection group. In addition, whole blood examination also found an increase in cytokines such as TNFα, IFNγ, IL-2, and IL-17, both Ag85A-specific, MVA-specific and total cytokines. In fact, in some cytokines, the aerosol vaccine induced significantly higher increases than the injectable vaccine.

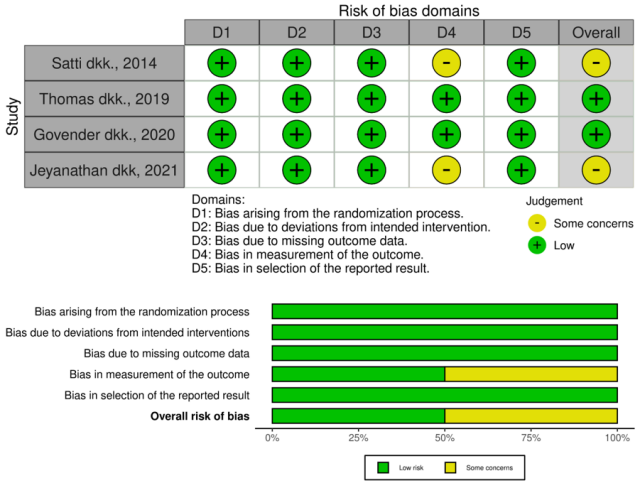

Figure 2: Risk of Bias Assessment of Included Studies Using RoB 2.0

Table II: Characteristics of Included Studies

Author, Year	Satti et al., 2014	Thomas et al., 2019	Govender et al., 2020	Jeyanathan et al.,2021
Country	UK	UK	Switzerland	Canada
Sample size	24	36	30	31
Group assignment	Group 1: AER (12) Group 2: ID (12)	Group 1: AER-ID (12) Group 2: ID-AER (12) Group 3: ID-ID (12)	Group 1: AER-SIM (10) Group 2: IM-SAER (10) Group 3: AER (10)	Group 1: LDA (11) Group 2: HDA (11) Group 3: IM (9)
Age (year)	18-50	21-42	21-54	18- 42
Vaccine type	MVA85A	MVA85A	ChAdOx 1-85A	AdHu5Ag85A
Doses	1x 10^7 PFU	5x10^7 PFU	10^{10} vp	LDA: 10^6 PFU HDA: 2x10^6 PFU IM: 10^8 PFU
Duration of intervention	24 Weeks	24 Weeks	24 Weeks	24 Weeks

Abbreviation: AER, Aerosol; ID, Intradermal; IM, Intramuscular; SIM, Saline Intramuscular; SAER, Saline Aerosol; LDA, Low-dose Aerosol; HDA, High-dose Aerosol.

Furthermore, the use of aerosolized TB vaccines is also considered safe in terms of side effects. The number of adverse event did not differ significantly between the injection and aerosol vaccination groups (p>0.05). Details of the comparison of immune responses and side effects from each study can be seen in Table III and Table IV.

DISCUSSION

Type of Tuberculosis Vaccine

The first tuberculosis vaccine developed was Bacille Calmette-Guŭrin (BCG). The vaccine is made from an attenuated strain of Mycobacterium bovis (12). The vaccine triggers the strengthening and activation

Table III: Immunogenicity Outcomes of Included Studies

Study (year)	Immunologic Parameter	Time-point	Key Finding (vs. Baseline or Inter-group)	p-value
Satti	NS IFNγ (all groups)	12 weeks post-vaccination	Significant increase	p < 0.05
	MVA-specific CD4+ IFNγ+	1 week post-vaccination	Significant response in aerosol group	p = 0.0469
		2 week post-vaccination	Significant response in aerosol group	p=0·0293
		2 week post-vaccination	Significant response in intradermal group	p=0·0352
			AUC aerosol group was significantly higher compared to intradermal group	p=0·0358
	MVA CD8+ T cell IFNγ+	2, 4, 12 weeks post-vaccination	Significant response in aerosol group	p < 0.05
		1-4 weeks post-vaccination	Significant response in intradermal group	p < 0.05
			AUC aerosol group compared to intradermal group didn't differ significantly	p=0·5319
	BAL CD4+ T cell cytokines	Varied	Higher in aerosol group (IFNγ, TNFα, IL-2, IL-17)	p = 0.033, 0.05, 0.04, 0.015
	WB CD4+ T cell cytokines	Up to 24 weeks	IFNγ & IL-2 significant longer in intradermal vs. aerosol (4/2 wks)	p < 0.05
		Up to 4/2 weeks	TNFα & IL-17 significant longer in intradermal vs. aerosol (2/1 wks)	p < 0.05
Thomas, 2019	NS IFNγ (all groups)	7 days post-prime vaccination	Significant response in all groups (G1, G2, G3)	p = 0.001, 0.004, 0.001
	NS IFNγ (inter-group)	7 days post-prime vaccination	G1* > G2 and G1* > G3	p = 0.017, 0.021
	NS IFNγ (all groups)	35 days post-boost	Significant response, G2* > G1 and G3	p = 0.002, <0.001
	MVA-specific CD4+ T cell	7 & 35 days	Significant response at various times for G1, G2, G3	p = 0.001, 0.042, 0.001
	MVA-specific CD8+ T cell	Day 42 vs 28	Significant increase for all groups (G1, G2, G3)	p = 0.027, 0.008, 0.009
	WB ICS: Ag85A-specific CD4+ IFNγ+	7 days post-prime	Significant in all groups; G1* > G2 & G3	p = 0.001, 0.004, 0.001; p=0.009, 0.008
	WB ICS: Ag85A-specific CD4+ TNFα+	Day 7 & 28	Significant for G1 (D7), G2 & G3 (D28); G1* > G2 & G3	p = 0.001, 0.039, 0.002; p=0.024, 0.009
	MVA-specific CD8+ IFNγ+	Day 14 & 168	Significant for G1 & G2 (D14), G2 (D168)	p = 0.020, 0.016, 0.016
	MVA-specific CD8+ TNFα+	Day 28 & 42	Significant for G1 on day 28 and 42	p = 0.002, 0.004
Govcnder	Ag85a: CD4+ IFNγ+	Day 0-168	G1: NS. G2: significant D16 & D28. G3: NS.	p > 0.05; p<0.05, p<0.01; p>0.05
	Ag85a: CD4+ IL-2+	Day 7-28	G1 & G3: significant D16 vs D7. G2: significant D28.	p < 0.01; p<0.05; p<0.01
	Ag85a: CD4+ TNFα+	Day 0-168	G1 & G3: NS. G2: significant D16 & D28.	p > 0.05; p<0.01, p<0.001
	Ag85a: CD4+ IL-17+	Day 0-168	G1, G2, G3: NS.	p > 0.05
	Ag85a: CD8+ IFNγ+	Day 0-168	G1 & G3: NS. G2: significant D28.	p > 0.05; p<0.05
	Ag85a: CD8+ TNFα+	Day 0-168	G1 & G3: NS. G2: significant D28.	p > 0.05; p<0.05

CONTINUE

Table III: Immunogenicity Outcomes of Included Studies (continued)

Study (year)	Immunologic Parameter	Time-point	Key Finding (vs. Baseline or Inter-group)	p-value
	Airways: Total cytokine+ CD4+ (Ag85A)	Week 2 & 8	LDA: increased vs baseline. HDA: increased W2. IM: NS.	p = 0.002, 0.003; p=0.002; p>0.05
	Airways: Single cytokine+ CD4+ (Ag85A)	Week 2 & 8	LDA: IFNγ, TNFα, IL-2 increased at W2 & W8.	p = 0.002/0.003; 0.001/0.005; 0.002/0.003
		Week 2	HDA: IFNγ, TNFα, IL-2 increased.	p = 0.004; 0.002; 0.006
Jeyanathan, 2021	Airways: Total cytokine+ CD8+ (Ag85A)	Week 2 & 8	LDA: increased vs baseline. HDA & IM: NS.	p = 0.01 (W2&W8); p>0.05; p=0.01 (W2)
	Airways: CD103+IFNγ+ (of CD4+)	Week 2 & 8	LDA: trend at W8. HDA: significant W2. IM: NS.	p = 0.0625; p=0.0391; p>0.05
	Airways: CD103+IFNγ+ (of CD8+)	Week 2	LDA: trend. HDA & IM: NS.	p = 0.0625; p>0.05
	Airways: CD49d+IFNγ+ (of CD4+), Peak	Peak response	LDA vs IM: trend. HDA vs IM: significantly higher.	p = 0.0519; p=0.0256
	Blood: CD49d+IFNγ+ (of CD4+)	Week 2	LDA & HDA: increased vs baseline. IM: NS.	p = 0.002; p=0.002; p>0.05
	Airways: Total cytokine+ CD8+ (Ag85A) IFNγ	Week 2	Significant increases for LDA, HDA and IM group	p=0.002; p=0.0273; p=0.007
		Week 4	Significant increase for LDA and IM group	p=0.003; 0.007
		Week 8	Significant increase for IM group	p=0.03
		NS	No significant increase for HAD group	p>0.05
	Airways: Total cytokine+ CD8+ (Ag85A) TNFα	Week 2	Significant increase for LDA and IM group	p=0.001; p=0.007
		Week 4	Significant increase for LDA and IM group	p=0.0391; 0.0391
		NS	No significant increase for HDA group	p>0.05
	Airways: Total cytokine+ CD8+ (Ag85A) IL-2	Week 2	Significant increase for LDA, HDA, IM group	p=0.0039; p=0.003; p=0.007
		Week 4	Significant increase for LDA, HDA, IM group	p=0.0078; p=0.007; p=0.007
		Week 8	Significant increase for IM group	p=0.023
		Week 16	Significant increase for IM group	p=0.023

Abbreviation:
NS: Non-specific; BAL: Bronchoalveolar lavage; WB: Whole blood; ICS: Intracellular cytokine staining; LDA/HDA: Low/High Dose Aerosol; IM: Intramuscular; G: Group; CD: Cluster of differentiation; IFNγ: Interferon-gamma; TNFα: Tumor necrosis factor-alpha; IL: Interleukin.
** Group with the higher result in that comparison. All statistical analyses are versus baseline (Day/Week 0) unless stated as an inter-group comparison.*

of the innate immune system, leading to changes in the expression pattern of the immune response. In addition, the BCG vaccine induces a memory T-cell response, where effector memory T-cells will secrete IFN-γ to activate macrophages so that they can destroy intracellular microbes (13). Furthermore, MVA85A is a vaccine candidate developed with Ag85A antigen and expressed using Vaccinia Ankara virus. This TB vaccination candidate was created as a BCG booster. The BCG prime-MVA85A boost vaccination can produce Th1 and Th17 antigen-specific T cells, which are thought to be crucial for TB prevention. ChAdOx1-85A is a chimpanzee adenovirus (ChAd) vector vaccine that expresses Ag85A. One of the characteristics of adenovirus is that its target site is in the lung, which is also the main site of Mycobacterium tuberculosis (14). The ChAd vector has the advantage of low levels of antibody neutralization against chimpanzee adenovirus (ChAd) in humans, making it a promising vaccine candidate (15). Then, the Ad5Ag85A vaccine is an adenovirus type 5-based viral vector vaccine that expresses the Ag85A antigen of Mycobacterium tuberculosis (16). Adenovirus has high immunogenic properties and can activate the innate and humoral immune systems. Intramuscular immunization of Ad5Ag85A triggers antigen-specific T-cell responses in the interstitium of the spleen and lung that can provide immune protection against the pathogen, making it a potential TB vaccine candidate (17).

The Potency of Aerosolized Vaccine

The significant results obtained are inseparable from the physiological and immunological advantages following the direct aerosol delivery of the TB vaccine to the respiratory mucosa via nebulizer. When administered as a single vaccination, as in the study by Satti et al. (2014), the aerosol vaccine significantly increased CD4+ IFNγ T cell MVA within the first week, faster than injection. On

Table IV: Safety Outcomes and Adverse Events of Included Studies

Study (Year)	Group (n)	AE Category	Specific AE	Number of Subjects
Satti et al., 2014	A: Aerosol MVA85A (n=12)	Systemic AEs (Mild, except 2 moderate headaches in aerosol group)	Fever	0
			Feverish	1
			Arthralgia	0
			Myalgia	0
			Malaise	2
			Fatigue	5
			Headache	5
			Nausea/Vomiting	1
	B: Intradermal MVA85A (n=12)	Systemic AEs (Mostly mild, no clinical difference between groups)	Fever	1
			Feverish	1
			Arthralgia	1
			Myalgia	2
			Malaise	2
			Fatigue	6
			Headache	5
			Nausea/Vomiting	*0*
Thomas et al., 2019	G1: Aerosol (n=12)	Local AEs (Day 0)	Local Erythema	0
			Local Swelling	0
			Local Scaling	0
			Local Pain	0
			Local Pruritus	0
			Local Warmth	0
			Axillary Pain	0
			Lymphadenopathy	0
		Respiratory AEs (Day 0)	Chest Pain	1
			Coughing Phlegm	0
			Shortness of Breath	2
			Sore Throat	2
			Cough	4
			Nasal Congestion	1
		Systemic AEs (Day 0)	Malaise	3
			Nausea	1
			Fatigue	5
			Headache	5
			Arthralgia	3
			Myalgia	5
			Feverish	2
			Fever	2
			Chills	1
			Presyncope	0
	G2: Intradermal (n=13)	Local AEs (Day 0)	Local Erythema	13
			Local Swelling	13
			Local Scaling	13
			Local Pain	12
			Local Pruritus	12
			Local Warmth	12
			Axillary Pain	2
			Lymphadenopathy	2

CONTINUE.....

Table IV: Safety Outcomes and Adverse Events of Included Studies

Study (Year)	Group (n)	AE Category	Specific AE	Number of Subjects
Thomas et al., 2019	G2: Intradermal (n=13)	Respiratory AEs (Day 0)	Chest Pain	0
			Coughing Phlegm	2
			Shortness of Breath	1
			Sore Throat	3
			Cough	4
			Nasal Congestion	0
		Systemic AEs (Day 0)	Malaise	4
			Nausea	0
			Fatigue	3
			Headache	6
			Arthralgia	2
			Myalgia	5
			Feverish	3
			Fever	1
			Chills	0
			Presyncope	2
Govender et al., 2020	\\G1: Aerosol (n=10)	Local AEs *(*p = 0.0093* vs IM)*	Pain	2
			Erythema	1
			Induration	0
			Other	0
		Respiratory AEs	Alveolar Leucocytosis	8
			Bronchial Inflammation	1
			Cough	0
			Dyspnea	0
			Sore Throat	3
			Chest Pain	0
			Other	4
		Systemic AEs	Fatigue	4
			Headache	2
			Feverish	2
			Myalgia	1
			Arthralgia	0
			Nausea	0
			Other	2
	G2: Intramuscular (n=10)	Local AEs *(Significantly higher)*	Pain	8
			Erythema	2
			Induration	1
			Other	1
		Respiratory AEs	Alveolar Leucocytosis	8
			Bronchial Inflammation	3
			Cough	0
			Dyspnea	0
			Sore Throat	4
			Chest Pain	0
			Other	2

CONTINUE.....

Table IV: Safety Outcomes and Adverse Events of Included Studies

Study (Year)	Group (n)	AE Category	Specific AE	Number of Subjects
Govender et al., 2020	G2: Intramuscular (n=10)	Systemic AEs	Fatigue	4
			Headache	4
			Feverish	0
			Myalgia	3
			Arthralgia	1
			Nausea	1
			Other	1
		Local AEs	Local Pain	0
			Redness	0
			Swelling	0
		Respiratory AEs	Cough	2
	G1: Low Dose Aerosol (n=11)		Runny Nose	3
			Sneezing	1
			Sinus Pain	1
			Shortness of Breath	0
			Nose Bleed	1
			Itchy Throat	0
		Systemic AEs	Fatigue	4
			Myalgia	3
			Headache	3
			Arthralgia	1
			Chest Pain	1
			Abdominal Pain	1
			Chills	2
			Dizziness	0
		Local AEs	Local Pain	0
Jeyanatahan et al., 2021			Redness	0
			Swelling	0
		Respiratory AEs	Cough	2
			Runny nose	2
			Sneezing	1
			Sinus Pain	0
	G2: High Dose Aerosol (n=12)		Shortness of Breath	1
			Nose Bleed	0
			Itchy Throat	1
		Systemic AEs	Fatigue	3
			Myalgia	0
			Headache	7
			Arthralgia	0
			Chest Pain	0
			Abdominal Pain	1
			Chills	0
			Dizziness	0
		Local AEs	Local Pain	0
	G3: Intramuscular (n=9)		Redness	1
			Swelling	1
Jeyanatahan et al., 2021	G3: Intramuscular (n=9)	Respiratory AEs	Cough	4
			Runny Nose	2
			Sneezing	2
			Sinus Pain	0
			Shortness of Breath	0
			Nose Bleed	0
			Itchy Throat	0
		Systemic AEs	Fatigue	3
			Myalgia	0
			Headache	2
			Arthralgia	1
			Chest Pain	0
			Abdominal Pain	2
			Chills	0
			Dizziness	2

CONTINUE.....

Table IV: Safety Outcomes and Adverse Events of Included Studies

Abbreviation:
AE: Adverse Event; G: Group; n: number of subjects in the group; IM: Intramuscular. Data presented as count of subjects experiencing the event. In Satti 2014, most systemic AEs were mild, with no clinical difference noted between groups

bronchoalveolar lavage (BAL) examination, CD4+ T cell cytokines also increased significantly more than those in the injection group. However, on Whole Blood (WB) examination, CD4+ IFNγ+ IL-2 T cells remained stable, increasing significantly longer in the injection group until week 24. Then, in a study by Thomas et al. (2019), in the first week, the group that received the aerosol vaccine as a primer showed a higher increase in BAL TNFα, IL-2, IL-17 than group that received the injection first. The opposite results appeared at week five or a week after administration of the booster vaccine. The group that received the vaccine injection as primary and aerosol as a booster obtained a significantly higher immune response. A notable difference in results was found in the study by Govender et al. (2020), which used the ChAdOx1-85A vaccine type, a significant increase in immune response was only obtained in the group that received the intramuscular injection vaccine and saline aerosol, except for Ag85a-specific CD4 + IL2 + which increased significantly in all groups. The last is the study by Jeyanathan et al. (2021); Airways total cytokine+ CD4 T cells increased significantly in both the low-dose and high-dose aerosol groups, with the increase remaining significantly stable longer in the low-dose aerosol group until week 8. Airways total cytokine+ CD8 T cells (Ag85A) only increased significantly in the low-dose aerosol and intramuscular groups. Then, when assessed over time and compared to baseline, IFNγ and IL-2 blood levels increased significantly in all groups.

Meanwhile, TNFα only increased significantly in the low-dose aerosol and intramuscular groups. Blood cytokine increases that remained stable significantly longer occurred in the intramuscular group until weeks 8 and 16. These four studies show that aerosolized TB vaccines are superior in enhancing the body's immune response in the respiratory tract. Details of the comparative immunogenicity effects of each study can be found in the appendix.

Safety and side effects

Three types of safety were distinguished between the aerosol and intradermal immunisation groups: systemic, respiratory, and local. Adverse events tended to be mild on average, with some moderate but they commonly happened after TB vaccination. A description of adverse events from each inclusion study is summarized in the appendix.

In the MVA85A vaccine, There was no difference in respiratory adverse events between the intervention and placebo groups. In both groups, respiratory adverse effects were rare and moderate. Respiratory symptoms were cough and sore throat. As for local symptoms, the intradermal group showed local reactions in the form of erythema, inflammation, and some other mild reactions. The first participant vaccinated with high-dose aerosolized MVA85A experienced a moderate vesicular skin rash on the right side of her face that appeared 11 days after vaccination. This rash was later diagnosed as herpes zoster (varicella-zoster virus) on the right C2 dermatome and was not detected in other participants (15). Systemic side effects were assessed after seven days of vaccine administration. Additionally, there was no difference between the two groups in this category. The most prevalent symptoms were mild to severe headache and mild fatigue. The only systemic symptom experienced by the aerosol group was nausea in one person.

In contrast, there were four people with symptoms only from the intradermal group, one with fever, another with joint pain, and the rest with muscle pain. Following vaccination, one person in each group experienced feverish symptoms. One individual who received the injection intradermally experienced a slight temperature (37.7°C) the night after the shot. In each group, three individuals experienced no systemic adverse effects attributable to the immunization (9).

The study by Thomas et al. (2019) divided the intervention into three MVA85A vaccine groups. That is, the group that received the aerosol route vaccine then intradermal, the second group received the intradermal route vaccine then aerosol, and the third group received the intradermal route vaccine then intradermal. In this study, no serious adverse events occurred. Local responses at the injection site following intradermal MVA85A immunisation were the most common adverse events across all groups. The majority of these intradermal vaccination-related local responses were modest. Respiratory side effects were also mild in all vaccination routes. The most common effects in some individuals in both groups were cough, sore throat, and shortness of breath. There were no differences in systemic side effects across routes. The most frequent adverse effects in all groups were fatigue, headache, and muscle soreness. All these side effects are temporary and fully resolved within six days (3).

Meanwhile, both the low and high doses of the AdHu5Ag85A vaccination administered intramuscularly or by aerosol inhalation were well tolerated and safe. Local reactions only occurred in the intradermal group, where two people had swelling and redness after injection. In every intervention group, respiratory adverse effects were uncommon, mild, brief, and comparable. Headache and exhaustion were the most frequent systemic adverse effects. In the group with the high-dose AdHu5Ag85A vaccine, there were seven people with headaches. This number was higher than the other groups: three in the intradermal group and two in the low-dose aerosol group (18).

In the ChAdOx1-85A vaccine, the majority of local adverse events occurred in the intradermal group, where eight people complained of pain and two others had skin erythema. There was no difference in respiratory adverse events between the groups, with the most common symptom being mild signs of lung inflammation on bronchoscopic examination that were not clinically significant. Those symptoms were the most common in the intradermal group, with three affected people. Nonetheless, one of the most prominent challenges in administering pulmonary vaccines is the risk of developing local hypersensitivity or intolerance, given the fragile nature of the lung mucosa. This has implications for setting the effective dose size or selecting appropriate inhalation techniques.

Further research is needed to characterize the vaccine for aerosol administration (19) adequately. At the same time, systemic effects occurred in all groups, mainly fatigue and headache. In the intradermal group, there were more headaches than in the aerosol group, namely, four people versus two people (11).

Strengths and limitation

This is the first systematic review to assess the efficacy and safety of aerosolized TB vaccines. We included studies from three different countries with transparent administration of the intervention. In addition, this review also discussed the administration of aerosolized TB vaccines in various doses. Unfortunately, none of the studies used Asian samples, so our review may not represent the entire population. The population used in all inclusion studies was also small as most inclusion studies were still in phase-one testing, with the primary outcome being safety. In addition, the findings from

the evaluation of bias possibility showed that two studies had a risk of bias of some concern because in domain four, there was a team of assessors who were not blinded to the intervention provided and there was no information on whether this affected the final results. Some of the sources used in this study are from more than the last five years, due to the lack of research on this topic. Suggestions for the future are to conduct more research using the same protocol and a comprehensive population with low heterogeneity.

Future Implications

This study demonstrates that aerosolized TB vaccines possess considerable potential for enhancing immune responses while minimizing the risk of significant side effects relative to injectable vaccines. Future implications encompass the advancement of more effective vaccines featuring optimal formulations and dosages, as well as their implementation in nations with a significant tuberculosis burden, particularly in remote regions with scarce medical personnel. The aerosol vaccination method may also be applicable to other respiratory diseases, including influenza and COVID-19. Additional clinical trials involving more diverse populations are necessary to validate its efficacy across various age and ethnic groups. Aerosolised TB vaccines, if demonstrated to be safe and effective, could be incorporated into national immunisation programmes, necessitating modifications to health policies and the acquisition of appropriate inhalation equipment. Further research may establish this vaccine as a pivotal advancement in the global strategy to eliminate tuberculosis and other respiratory diseases.

CONCLUSION

The findings of our systematic review suggest that aerosolized TB vaccines exhibit significant potential for development regarding their effectiveness and safety. The significant immunogenicity findings across included studies and the absence of severe adverse events support this conclusion. Further comprehensive follow-up studies utilizing larger and more homogeneous samples are necessary to ascertain the applicability of aerosolized TB vaccines' effectiveness and safety across the entire population.

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