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The Front Line of Defense: Summary of the Efficacy of a Novel Intranasal Vaccine Formulation against Respiratory Threats in a Forward Deployed Military Setting

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Abstract

Background: Forward-deployed military troops are at high risk for acute respiratory infections (ARIs), an age-old and continuing challenge to operational readiness. Conventional intramuscular (IM) vaccines, which induce mostly systemic immunity, offer less than optimal protection at the mucosal portals of pathogen entry.

Aim: This review synthesizes current evidence of the effectiveness of novel intranasal (IN) vaccine technologies against respiratory threats, with specific focus on their application in a forward-deployed military environment.

Methods: A Systematic literature review was conducted in PubMed, Scopus, and Web of Science (2000-2024). Key search terms utilized were "intranasal vaccine," "mucosal immunity," "military personnel," "respiratory infection," "serological testing," and "PCR."

Results: Research has demonstrated that IN vaccines, particularly the live-attenuated and adenoviral vector vaccines, have a strong mucosal immune response characterized by tissue-resident memory T-cells and secretory IgA. Such a response outperforms IM vaccines in primary infection and transmission prevention. Logistically, IN delivery has numerous advantages of deployment, including simplicity of use and absence of needles. Evaluating effectiveness requires an integrated model that combines laboratory aspects (serology and PCR) with nursing activities (administration, adverse event tracking, and disease surveillance).

Conclusion: New formulations for IN vaccines possess vast potential to protect forces in the field. Their sterilizing immunity and operational benefit make them an important future asset. Success depends on an entirely integrated framework that leverages diagnostics and clinical expertise to guard force health and mission preparedness.

Keywords: Intranasal Vaccine, Mucosal Immunity, Military Medicine, Force Health Protection, Respiratory Pathogens, Serology, PCR, Nursing Surveillance.

1. Introduction

History's record of war is replete with episodes in which infectious disease decimated armies with greater violence than their enemies (Biselli et al., 2022). Even in the modern age, acute respiratory infection (ARI) remains the single largest threat to military readiness for operations. Operational environments of deployment, which have their high-density living quarters for troops, extreme physical and emotional stress, changing environmental temperatures and humidity, and potential exposure to novel pathogens, create a mise-en-scène for the extensive transmission of respiratory viruses and bacteria (Korzeniewski et al., 2015). ARI is projected to account for a high percentage of total medical visits and missed duty days during combat operations, directly impacting compromised mission capability (Sanchez et al., 2015).

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The backbone of ARI prevention in the military has been parenteral, most often intramuscular (IM) immunization. The trivalent inactivated flu vaccine (IIV), for example, is administered annually. While beneficial in reducing disease severity, IM vaccines create a systemic, humoral immune response with the production of circulating Immunoglobulin G (IgG) antibodies. This response is less effective at inducing the first line of defense at the mucosal surface of the upper respiratory tract, where pathogens initially begin to cause infection (Lund & Randall, 2021). Therefore, one can become infected, transmit the virus, and infect others, yet themselves remain free from severe clinical disease. This limitation highlights the need for a vaccine regimen that induces "sterilizing immunity" and avoids infection and transmission altogether.

Mucosal immunity, particularly for the respiratory tract, is maintained by a multi-component system that involves secretory Immunoglobulin A (sIgA), tissue-resident memory T-cells (Trm), and innate immune function (Mestecky et al., 2015). Intranasal (IN) vaccination is optimally designed to stimulate this local immune response. Through the targeting of antigens to the nasal-associated lymphoid tissue (NALT), IN vaccines have the ability to produce a powerful and localized reaction at the point of original pathogen entry (Heaney et al., 2024). "Novel" IN formulations, the focus here extends beyond commercial live-attenuated influenza vaccine (LAIV) to include systems such as adenovirus-vectored, protein subunit, and nanoparticle-based vaccines, and that often utilize novel adjuvants to enhance immunogenicity.

An in-depth evaluation of this new vaccine within a deployed military setting necessitates a multi-disciplinary response. This is based on the integration of three core components: a laboratory component involving serology to quantify immune response and PCR to confirm infections; a nursing component with responsibilities for vaccine administration, adverse event reporting, and clinical surveillance; and the larger security force objective of unit cohesion and mission accomplishment by preventing diffuse, incapacitating disease. This review will synthesize current evidence for the science of IN vaccines, outline the joint model of laboratory and nursing functions in a field study, discuss the operational advantages for use in the military, and examine the problems and future outlook of this promising technology.

The Scientific Basis for Intranasal Vaccination

Parenteral IM vaccines are very efficient at provoking an immune response to the visible signs of a systemic infection. They evoke strong IgG responses and circulating memory T and B cells. However, their ability to trigger a strong frontline defense in the upper respiratory mucosa is impaired (Belyakov & Ahlers, 2009). IgG is also able to transudate into the mucosal surfaces, but at reduced concentrations relative to locally produced sIgA. IM vaccination is also not highly effective in eliciting tissue-resident memory T-cells (Trm) in the airway. Trm cells play a critical role in the rapid control of a pathogen upon re-exposure as a key second line of defense against an ineffective mucosal antibody response (Schenkel & Masopust, 2014). This immune shortfall is the basis on which individuals vaccinated with IM constructs can nevertheless become infected with and transmit wild-type virus, perpetuating chains of transmission within a closed cohort (Baguelin et al., 2013).

The effectiveness of intranasal (IN) vaccines is founded on their unique ability to stimulate the respiratory tract's sophisticated mucosal immune system. The latter relies on key players that intercept the pathogens at the entry point. The most significant among them is secretory IgA (sIgA), the primary antibody found in mucosal secretions that neutralizes pathogens and inhibits them from binding to epithelial cells (Ceglia et al., 2023). In addition, tissue-resident memory T-cells (Trm) take up long-term residence in

tissues such as the nasal epithelium, offering an immediate response that includes infection when re-exposure occurs (Cheon et al., 2023). Intranasal vaccination addresses the inductive site for this immunity, the nasal-associated lymphoid tissue (NALT), directly since it is densely populated with immune cells poised to launch a vigorous, local response (Kiyono & Fukuyama, 2004).

To exploit this system, a number of vaccine platforms are being developed. Live-attenuated and replication-capable vectors like the licensed FluMist® cause intense immune stimulation by growing with a bare minimum without causing disease (Ye et al., 2022). Alternatively, non-replicating ones, such as protein subunit and virus-like particle (VLP) vaccines, are treasured for their safety but are often in need of mucosal adjuvants in order to elicit a robust IgA and T-cell response (Liang et al., 2024). Finally, nanoparticle vaccines are a potential answer by encapsulating the antigens and enhancing their presentation to immune cells, which can be engineered for broader safety against variant strains (Bezbaruah et al., 2022). Table 1 and Figure 1 illustrate the intramuscular (IM) vs. intranasal (IN) vaccine platforms for respiratory pathogens.

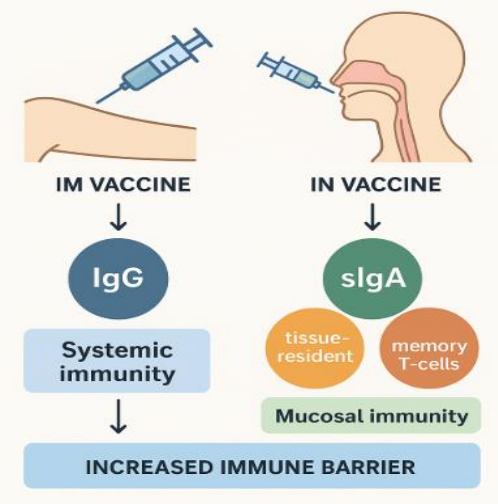

Figure 1. The mechanistic overview of the intramuscular (IM) vs. intranasal (IN) vaccine platforms for respiratory pathogens.

Table 1: Intra-muscular (IM) vs. Intranasal (IN) vaccine platforms for respiratory pathogens.

Feature	Intramuscular (IM) Vaccine	Intranasal (IN) Vaccine
Primary Immune Response	Systemic IgG, circulating memory cells	Mucosal sIgA, tissue-resident memory T-cells, systemic IgG
Site of Action	Draining lymph nodes	Nasal-Associated Lymphoid Tissue (NALT)
Sterilizing Immunity	Limited; reduces severity but not necessarily infection/transmission	High potential; aims to block infection and transmission at the portal of entry
Ease of Administration	Requires trained personnel, needles, syringes	Potentially easier; can be administered by nurses or self-administered
Logistical Footprint	Cold chain, sharps disposal required	May have less stringent cold chain requirements for some formulations
Acceptability	Needle phobia can be a barrier	Generally higher acceptability, especially in mass campaigns
Key Challenges	Poor mucosal immunity, need for annual reformulation (e.g., flu)	Risk of vaccine-associated symptoms, potential for pre-existing immunity to vectors (e.g., Ad5)

An Integrated Model for Assessing Effectiveness in a Deployed Environment

The extensive field testing of a novel intranasal (IN) vaccine in deployed military personnel

demands a sophisticated, integrated model that unites demanding laboratory science and diligent clinical care in synergistic balance. This three-legged stool—laboratory analysis, nursing administration, and operational oversight—constitutes a closed-loop system critical to determining true vaccine efficacy under challenging field conditions.

Laboratory Component: Quantifying Immunogenicity and Infection

The laboratory offers the objective foundation for vaccine assessment, providing quantitative readouts of immune response and real-world effectiveness. It begins with comprehensive baseline serological profiling, where pre-vaccination blood and mucosal samples (nasal wash and saliva) establish individual baseline levels of IgG and IgA specific to the pathogen. This critical first step enables distinction between pre-existing immunity and genuine vaccine-induced immune responses (de Silva et al., 2017). Post-vaccination, sophisticated laboratory techniques take over. Enzyme-linked immunosorbent assays (ELISAs) and multiplex immunoassays measure quantitatively the fold-increase in antigen-specific IgG and IgA titers at pre-determined timepoints (typically 28 days, 90 days, and 6 months post-vaccination). While serum IgG is an indicator of successful systemic immunization, the discovery of mucosal IgA in nasal secretions is the primary correlate of local protection at the pathogen entry point (Tsoi et al., 2015). For influenza-specific vaccines, hemagglutination inhibition (HAI) assays remain the gold standard for quantifying functional antibodies that neutralize the virus (Trombetta & Montomoli, 2016). Besides humoral immunity, state-of-the-art cellular immune monitoring employs enzyme-linked immunospot (ELISpot) and intracellular cytokine staining assays on peripheral blood mononuclear cells (PBMCs) to quantify virus-specific T-cell responses, including those with tissue-homing potential that is relevant to mucosal protection (Brekke et al., 2014; Ascough et al., 2019).

To complement serology, molecular diagnostics provide direct evidence of vaccine efficacy against infection. Active surveillance protocols mandate that all personnel who have symptoms of acute respiratory infection (ARI) be tested by multiplex PCR, enabling precise quantitation of the vaccine's ability to prevent clinical illness (Chen et al., 2024). Furthermore, routine PCR screening of asymptomatic personnel through scheduled surveillance picks up the impact of the vaccine on viral shedding and subclinical infection—both indicators of sterilizing immunity and transmission blockade (Lalani et al., 2021).

Nursing Component: Clinical Implementation and Surveillance

The nurse corps is the operational backbone that transforms laboratory protocol into field success. Nursing responsibilities involve the technically correct administration of a vaccine by initially making a proper delivery to the nasal-associated lymphoid tissue (NALT) via the correct utilization of spray devices. This technical competence extends to thorough patient education regarding vaccine expectations and side effects (Abdu Asiri et al., 2025). Vigilant safety monitoring is yet another paramount nursing function. Structured post-vaccination observation protocols mandate direct monitoring for immediate reactions during the first 15-30 minutes, followed by systematic recording of solicited and unsolicited adverse events using standardized electronic diaries or applications for defined periods (typically 7 days for local reactions and 28 days for systemic events). This meticulous documentation allows for early identification and management of serious adverse events (Wilson et al., 2020). Apart from administration and oversight of safety, nurses organize the clinical surveillance system. Nurses create and implement standardized case definitions for

ARI, operate sick-call systems, conduct clinical evaluations of symptomatic personnel, collect nasopharyngeal swabs for PCR testing, and maintain longitudinal databases that record all episodes of respiratory illness—including symptom severity, symptom duration, and impact on duty status (light duty, bed rest, etc.) (Beshbishy, 2024).

The powerful combination of laboratory diagnostics and nursing vigilance constitutes a comprehensive evaluation mechanism. The alignment of intricate clinical information and demanding laboratory findings yields a multidimensional portrait of vaccine activity, ranging from molecular immunogenicity through functional efficacy in reducing respiratory disease burden. The ultimate security objective of this combined approach is the preservation of unit integrity and mission accomplishment by preventing debilitating illnesses through state-of-the-art immunological defense (Table 2). Figure 2 illustrates the integrated laboratory–nursing model for evaluating intranasal vaccines in a deployed military context.

Table 2. Integrated Functions within a Deployed Military IN Vaccine Trial

Phase	Laboratory Role	Nursing Role	Operational Outcome
Pre-Deployment (Baseline)	Collects baseline serum & mucosal samples for IgG/IgA; performs baseline PCR screening.	Administers first dose of vaccine; educates personnel on AE reporting; obtains informed consent.	Establishes a healthy, characterized cohort.
Deployment (Monitoring & Surveillance)	Processes post-vaccination serology samples; runs PCR on all symptomatic swabs; analyzes data on immunogenicity and infection rates.	Administers booster dose if required; actively monitors for and documents AEs; conducts sick call, assesses ARI cases, and collects swabs.	Maintains real-time force health surveillance; provides immediate clinical care.
Post-Deployment (Analysis)	Compiles final immunogenicity data; performs statistical analysis on infection rate differences between vaccine and placebo groups.	Finalizes clinical illness database; reports on aggregate AE data and ARI outcomes.	Generates a comprehensive effectiveness report to inform future military vaccine policy.

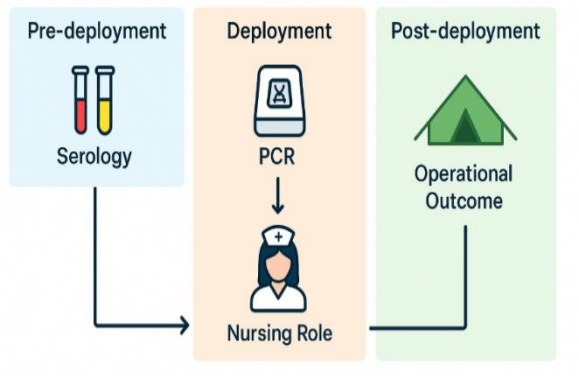

Figure 2. Integrated Model for Deployed Setting

This integrated model demonstrates that laboratory and nursing functions in tandem yield a firm basis for assessing novel vaccine platforms in the field setting, with the long-term strategic objective of maintaining military readiness through innovative force health protection.

Operational Advantages for Deployed Military Forces

Deploying an effective intranasal (IN) vaccine platform provides military forces with groundbreaking strategic and operational advantages

that extend far beyond individual health advantages. These advantages translate directly into enhanced force protection capabilities in three critical areas: mission assurance, logistics efficiency, and biodefense readiness.

Enhanced Force Health Protection and Mission Assurance

The most important functional advantage of IN vaccination is the potential to establish sterilizing immunity at the unit level. Unlike conventional intramuscular vaccines that primarily reduce disease severity, IN vaccines target mucosal immunity at the initial portal of pathogen entry. This has the effect of preventing both the initiation of infection and subsequent transmission among personnel. The operational impact is profound: by preventing outbreaks at their source, IN vaccines conserve valuable manpower and preserve unit integrity through deployment cycles. This function is particularly important for specialized units such as special operations forces, aviation teams, and intelligence units, where the incapacitation of even a small number of mission-critical personnel can render an entire unit inoperable. Sustained unit strength through effective prophylaxis translates directly into continued operational tempo and mission success rates, which corrects a long-standing pre-eminent cause of non-combat attrition in military operations (Grabenstein & Winkenwerder, 2004).

Logistical and Practical Superiority in Resource-Constrained Environments

Vaccines revolutionize the logistical footprint of vaccine programs in deployment settings. The needle-free injection system removes a number of logistical challenges simultaneously: it eliminates the necessity for syringes, sharps waste containers, and the associated biomedical waste management systems. This reduction of the medical waste streamlines supply chains and effectively eliminates needlestick injury risks, a significant occupational hazard in field medical care (Ledesma-Feliciano et al., 2023). The delivery regimen itself is a force multiplier—IN simplicity allows for swift mass immunization by limited medical personnel, with the possibility of delegation to trained non-medical personnel or even self-administration in emergencies. Such flexibility is priceless in large-scale deployments, outbreak containment, or when medical assets are thinly stretched. Furthermore, vaccine formulation innovation is also generating increasingly thermostable IN platforms that effectively eliminate cold chain requirements, a logistics bottleneck that routinely degrades vaccine feasibility in austere operational contexts. The ability to maintain vaccine stability across temperatures dramatically enhances dissemination prospects to forward operating bases and long-range patrols where refrigeration is minimal or nonexistent (Nguyen et al., 2022).

Rapid Response Capability for Emerging Biological Threats

The platform technologies upon which the majority of IN vaccine candidates are founded, particularly adenoviral vector systems, allow for unprecedented responsiveness to new biological threats. The "plug-and-play" character of these systems allows for the rapid development and deployment against novel pathogens through the insertion of genetic material from emerging threats into pre-existing, well-characterized delivery platforms. The strategic implication is a dramatically shortened timeline from pathogen identification to vaccine availability—a critical advantage in facing emerging influenza strains, SARS-like viruses, or bioengineered threats (Feng et al., 2025). Being able to immunize an entire deployed force against a novel pathogen rapidly is a paradigm shift in military biodefense, transforming the response from reactive containment to proactive protection. This capability not only sustains operational effectiveness in the case of biological attacks but also serves as a powerful

deterrent to the deployment of biological weapons by hostile forces.

The synergism of these advantages—preserved unit integrity, reduced logistical burden, and rapid response capability—establishes IN vaccination as a pillar of next-generation force health protection. By addressing both traditional respiratory threats and emerging biological threats through an effective, efficient delivery platform, IN vaccines have the potential to significantly contribute to military resilience and operational performance across the full spectrum of deployment environments (Hazazi, 2025).

Challenges, Limitations, and Future Directions

Despite their huge potential, the development and delivery of novel intranasal (IN) vaccines are confronted by challenges that must be strictly overcome. Most prominent among them is the safety profile; the intimate anatomical proximity of the nasal mucosa with the olfactory nerve calls for theoretical caution against entry of vaccine components into the central nervous system. Although existing vaccines like LAIV have spotless safety records, each new platform and adjuvant will need to undergo intense scrutiny. This is underlined by previous experiences, which include reports of a certain IN vaccine being associated with sporadic Bell's Palsy, underscoring the absolute necessity of diligent post-marketing surveillance (Madkhali et al., 2024; Mutsch et al., 2004).

Furthermore, pre-existing immunity can be a significant obstacle, particularly for viral-vectored vaccines, in the sense that immunity to the vector itself will suppress the immune response to the target antigen. Overcoming this will necessitate the use of rare human serotypes or non-human primate vectors (Fallatah et al., 2024). From a regulatory standpoint, the pathway to licensure for mucosal vaccines is less established than for injectable vaccines. Among the biggest hurdles will be the definition and verification of specific correlates of protection, such as a mucosal IgA threshold, that are required for regulatory licensure (Plotkin, 2023). Finally, successful implementation in an operational military setting demands careful planning, large-scale training of medical staff, and robust communications networks for adverse event reporting (Blackbourne et al., 2012).

Looking to the future, research aims to overcome these limitations and enhance the promise of IN vaccines. An important goal is the development of universal vaccines that possess the ability to offer wide protection against whole virus families, e.g., all influenza A viruses or beta-coronaviruses. Another possibility is that antigens from a number of pathogens could be included in one IN preparation, which would revolutionize vaccination regimens for deployed military personnel, offering broad-spectrum protection with one intervention (Wang et al., 2024).

Conclusion

The threat of respiratory diseases to military operational effectiveness is persistent and profound. The conventional intramuscular method of vaccination, while beneficial, has inherent immunological limitations that fail to prevent the establishment of infection and transmission of pathogens within closed cohorts. An intranasal vaccine formulation is a paradigm-changing response, leveraging the power of mucosal immunity to establish a potent frontline defense at the precise point of pathogen entry. The effectiveness of a vaccine in a deployed military population cannot be determined in isolation. It needs an integrated, multidisciplinary model wherein laboratory scientists accurately measure immune response and infection incidence, and military nurses implement the vaccination campaign, monitor safety, and record clinical outcomes. This synthesis of laboratory data and clinical surveillance yields the evidence base necessary to confirm the vaccine's contribution to force health protection.

The potential dividends are huge: not only improved protection against disease in the form of sterilizing immunity, but also significant operational and logistical advantages in challenging deployment environments. While safety, immunogenicity, and regulatory concerns remain, the strategic imperative of safeguarding the health of security forces makes the advancement of next-generation intranasal vaccine platforms a pressing priority for military medicine. By bridging immunology, diagnostics, and clinical practice, this collaborative effort offers a promising means for rendering the deployed force more resilient against one of its oldest and most persistent foes—the respiratory pathogen.

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