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Review Article

Pharmacovigilance Challenges in Intranasal Vaccines: A Comparative Perspective from CDSCO, USFDA, EMA, and ANVISA

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ABSTRACT

Intranasal vaccines have been used for seasonal influenza, and more recently, for SARS-CoV-2. However, they also pose unique safety risks not typically associated with injectable vaccines, such as nasal irritation, mucosal inflammation, altered olfactory function, and respiratory complications in younger children. Despite global use, pharmacovigilance frameworks for intranasal vaccines differ substantially across countries. These inconsistencies limit the ability to compare safety profiles, harmonize response strategies, or conduct global signal detection. Understanding these region-specific and overlapping challenges is essential for advancing safe mucosal vaccine development and deployment. To identify and compare pharmacovigilance challenges in intranasal vaccines in India, USA, EU and Brazil. A structured narrative review methodology was used involving the systematic search of WHO-VigiBase, Eudravigilance and VAERS databases. Peer-reviewed publication, regulatory guidance and vaccines safety databases were synthesised. Regulatory gap matrix was identified to map the surveillance differences across agencies. Analysis revealed substantial variability in the maturity, digital infrastructure, and responsiveness of pharmacovigilance systems across the four agencies. Intranasal vaccines present promising advancements in vaccine delivery; however, their unique safety profiles require enhanced vigilance. CDSCO, USFDA, EMA and ANVISA face distinct regional PV challenges but share common limitations in reporting completeness.

Keywords: Intranasal Vaccines, Mucosal Immunity, Pharmacovigilance, Post-Marketing Surveillance, Regulatory Science, Vaccine Safety.

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INTRODUCTION

Intranasal vaccines-commonly termed nasal vaccines-are increasingly regarded as a preferable alternative to traditional parenteral routes due to their simplicity and user-friendly mode of delivery. One of the most significant advantages of this approach is the ability of the individual to give the vaccine without the need for trained personnel, thus making it more accessible. Secondly, the intranasal route allows for the direct targeting of the mucosal surfaces of the nasal cavity, which are the main entry points for most respiratory infections. Thus, the intranasal route is most effective in eliciting an immune response that can protect the body against infections such as influenza and more recently, COVID-19.[1]

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Live Attenuated Influenza Vaccines, such as FluMist and Fluenz Tetra, are the most widely used intranasal vaccines globally. Post-marketing data have identified age-specific risks, including increased wheezing in children under two years and reduced effectiveness in certain influenza seasons. FluMist, a live attenuated trivalent or quadrivalent Influenza Virus Vaccine (LAIV) authorized by FDA, was created to prevent seasonal influenza infections. It contains two influenza B strains in addition to the influenza A viruses H1N1 and H3N2.[2-4] Bharat Biotech International recently approved the iNCOVACC recombinant vaccine for restricted use in emergency situations in India. The vaccine is delivered through the nasal route in the form of nasal drops. These nasal vaccinations creation and licensure to prevent COVID-19 have changed the game globally.[1,5]

Similarly, the intranasal influenza vaccine Fluenz, which has been licensed by the European Medicines Agency, made up of four live attenuated strains of influenza virus (H1N1, H3N2, and two influenza B viruses) and is intended to prevent influenza infection in humans.[3,6]

Regulatory agencies maintain differing PV systems: the USFDA relies on the BEST initiative, Vaccine Adverse Event

Reporting System (VAERS), which functions as a passive/spontaneous reporting platform for collecting post-vaccination safety data. Reports submitted to VAERS are forwarded to the Uppsala Monitoring Centre-WHO's designated global hub for drug and vaccine safety surveillance-to support international pharmacovigilance initiatives. This process allows the United States to contribute vaccine safety information to a worldwide network of countries that also rely on passive monitoring systems.[7,8]

The EMA operates EudraVigilance and mandates Enhanced Safety Surveillance (ESS) for influenza vaccines.[9] The EudraVigilance Post-Authorization Module serves as a centralized database for collecting all the suspected serious adverse reaction reports related to medicinal products, including vaccines, that hold marketing authorization within the European Union. Both pharmaceutical companies and regulatory authorities across the European Economic Area are required to submit these reports electronically to EVPM and must do so within 15 days of receiving the information.[10]

The Brazilian government regulates medication use through the National Health Surveillance Agency (ANVISA). ANVISA emphasizes the importance of a sensitive surveillance system to assess the safety of the product and quickly address public concerns to effectively manage Adverse Event Post Vaccination (AEPV).[11] The Drug Vigilance Centre (VigiMed) is the pharmacovigilance system used by the Brazilian health regulatory Agency. The Uppsala Monitoring Centre (UMC) developed a Web-based system for managing individual case safety Reports (ICSR).[12]

METHODOLOGY

This study employed a structured approach that is specifically tailored for comparison of pharmacovigilance systems in different regulatory agencies.[13]

A wide search was undertaken through various online resources including PubMed and Google scholar. Literature sources from regulatory agency websites (CDSCO.gov.in, FDA.gov, EMA.europa.eu, ANVISA.gov.br) and the Global Vaccine Safety.[4,5,14]

The design for narrative review was selected as appropriate approach for synthesizing heterogenous evidence from regulatory documents, peer-reviewed literature and institutional pharmacovigilance reports from different countries.

The search strategy included combination of keywords such as: 'Intranasal vaccines', 'nasal vaccines', 'pharmacovigilance', 'vaccine safety', 'adverse events following immunization', 'VAERS', 'Eudravigilance', 'Vigibase', 'CDSCO', 'USFDA', 'ANVISA'.[12]

The inclusion criteria comprised: (i) Peer-reviewed research articles, (ii) regulatory guidelines and official documents, (iii) pharmacovigilance database reports, (iv) studies focusing on vaccine safety, pharmacovigilance, or intranasal vaccine surveillance and (v) Publications available in English language.[12]

The exclusion criteria included: (i) Non-english publication, (ii) conference abstracts without full-text availability, (iii) Studies not related to vaccines or pharmacovigilance, (iv) Duplicate records.[13]

The literature search was performed using studies from 2000 to 2025 to include studies that were done both at the inception of intranasal vaccines and recent progressions, especially during the time of COVID-19 pandemics.[3,15]

An analysis framework based in a gap matrix was devised for analyzing the difference between the pharmacovigilance systems of different regulators, which included the Central drugs standard control organization, U.S Food and drug administration, European medicines agency and Agencia Nacional de vigilancia Sanitaria. The analysis framework involved the analysis of various parameters of the pharmacovigilance system, such as reporting systems, Risk management plan, signal detection capabilities, database integration, accessibility to the public and regulatory harmonization.[13,16]

Ethical Statement

This study is a Structured narrative review based on published literature, regulatory guidelines, and publicly accessible pharmacovigilance databases. No human participants, animals, patient data or identifiable personal information were involved in the conduct of this study. Hence, no Ethical approval and informed consent was required.

RESULTS

All four agencies operate under different legal mandates, utilize different pharmacovigilance databases, timelines and methodologies for signal detection which makes international harmonization for intranasal vaccine safety monitoring challenging.[16]

Adverse events in intranasal vaccines

For the trivalent LAIV, FluMist, the safety surveillance through VAERS after licensure for the first two years of use from August 2003 to July 2005, covering 2.5 million vaccine recipients, revealed 460 adverse event reports, including 7 possible anaphylaxis cases, 2 cases of Guillain - Barre syndrome, 1 case of Bell's Palsy, 8 cases of asthma exacerbation in individuals with previous history of asthma, with no fatalities reported (Table 1).[20]

The FluMist Quadrivalent package inserts documents post approval spontaneous reports of the following neurological adverse events, Guillain - Barre syndrome, Bell's palsy, Meningitis, and Eosinophilic Meningitis, as well as immune system disorders including anaphylaxis and facial oedema.[21]

The EMA-approved vaccine Fluenz Tetra (Quadrivalent live attenuated influenza vaccine) has shown a well characterized pattern of adverse events in nine consecutive seasons of enhanced safety surveillance in England from 2014 to 2023. A prospective pilot cohort study on safety of Fluenz tetra vaccine in children and adolescents in 2014 - 2015 season found the incidence of wheezing rates were 30 times higher in children with asthma than in those without asthma.[22]

India's approved Intranasal vaccine - iNCOVACC (BBV154) - was found to have been generally well tolerated by adult, with no pain associated, unlike when using intramuscular injections of control vaccines, while having a superior humoral neutralizing response in comparison to control vaccines, specifically in relation to the ancestral trial SARSCoV-2 virus (Table 2).[23]

The regulatory gap matrix indicates significant disparities in pharmacovigilance capabilities and operational capacity among the regulatory bodies. The FDA and EMA exhibit highly sophisticated alert detection mechanisms and risk management process, while the CDSCO and ANVISA have deficiencies in terms of their reporting, transparency and digitization capabilities. These regulatory gaps could potentially affect global surveillance and alert detection for intranasal vaccines.[13,16]

A major difference is in signal detection, whereby Eudravigilance makes use of sophisticated statistical methods in validating signals, while VAERS depends mostly on passive surveillance systems, hence requiring validation using other such as BEST. This difference affects the effectiveness in detecting safety signals.[7,10]

There are differences even in terms of Risk management planning. While the European union requires RMP submission and constant updates, India adheres to partially implemented framework under NDCT Rules 2019 and Brazil maintains a relatively basic structure, potentially leading to inconsistencies in post-marketing surveillance outcomes.[13,16]

Data transparency and availability differentiate these systems, as there is greater availability of pharmacovigilance data to the public in the U.S and Europe, allowing for independent assessment of data, while lower data availability in India will lead to delayed safety communication and lack of independent assessment.[13,24]

DISCUSSION

The immunization process involved in an intranasal vaccine is inherently different from that of an intramuscular vaccine and possesses challenges for standard safety evaluation. The upper respiratory tract uses SIgA antibodies for mucosal defense but other vaccines such as intramuscular and intradermal vaccines cause an IgG reponses but fail to effectively induce mucosal IgA. Unlike conventional intramuscular vaccines, which primarily elicit systemic response with limited mucosal protection, nasal vaccines produce SIgA at the place where pathogen enters the body and engage common mucosal immune system to promote activated immune cells to distant mucosal sites.[26]

The comparative analysis of pharmacovigilance frameworks of CDSCO, USFDA, EMA, and ANVISA showed considerable heterogeneity in regulatory infrastructure, AEs reporting, Signal detection, and Intranasal vaccines specific surveillance, which is in line with previous comparative analysis of pharmacovigilance of various agencies.[12,16]

India's Pharmacovigilance program of India system faces challenges with the healthcare worker awareness of adverse event following immunization reporting obligations, particularly among the private practitioners at the primary care level.[24]

However, as a passive surveillance system, there is an inherent limitation in VAERS in that it is not possible to ascertain causality

Table 1: Pharmacovigilance framework parameters for intranasal vaccines.[1,4-6,15-19]

Pharmacovigilance parameter	India	United states	Europe	Brazil
Legal framework	Central Drugs Standard Control Organisation (CDSCO).	Food and Drug Administration (FDA).	European Medicines Agency (EMA).	Agência Nacional de Vigilância Sanitária (ANVISA).
Clinical trial authorizeation	All vaccines are classified as 'new drugs' requiring manufacturing permission from CDSCO before licensing.	Investigational New Drug (IND) application required before clinical trials, FDA oversight at each phase.	Clinical Trial Application (CTA) to national competent authorities; EudraCT registration required.	ANVISA Permission required per RDC No. 945 and RDC No. 705.
Approved Intranasal vaccines	BBV154 (iNCOVACC) COVID-19 vaccine by Bharat Biotech.	FluMist Quadrivalent live attenuated influenza vaccine.	Fluenz Tetra (Quadrivalent).	None currently approved

Table 2: Regulatory Gap Matrix for Pharmacovigilance systems in intranasal vaccines.[13,16,24,25]

Parameters	India	United states	Europe	Brazil	Identified Gap
Adverse event reporting system	PVPI	VAERS	Eudravigilance	Vigimed	Underreporting in India and Brazil
RMP requirement	Partial, NDCT rules 2019	Mandatory; REMS System	Mandatory; EU RMP guideline	Basic:RDC 406/2020	Inconsistent RMP enforcement
Database Integration	Limited	Strong	Integrated EU network	Moderate	Poor global data integration
Signal detection	Basic	Semi-automated	Advanced statistical tools	Limited capacity	Lack of advanced analytics in India and Brazil.
Intranasal vaccine surveillance	Emerging	Established	Established	Not available	Lack of experience in Brazil
Regulatory Harmonization	Limited	Moderate	Strong	Limited	No global harmonized PV systems
Data Transparency	Low	High	High	Low	Limited Public access in India and Brazil.

between adverse events and vaccination, and results obtained from VAERS data need to be interpreted with caution to avoid any erroneous conclusions.[7]

The large volume of COVID-19 vaccine-related ADR reports submitted to the Eudravigilance database was shown to reduce the statistical signal strength of 15 out of 52 re-evaluated signals, and the large volume of ADR reports was shown to impact routine statistical signal detection activities.[25]

Brazil's VigiMed which was established with the agreement of ANVISA and the Uppsala Monitoring Centre, serves as the pharmacovigilance platform for international medicines monitoring, with the reported adverse events being assessed for severity, causality and risk.[11]

Intranasal vaccines are associated with safety risks pertaining to respiration, particularly in pediatric population. Several clinical trials and post-market surveillance have reported a higher rate of wheezing and exacerbation of asthma among children who have been administered intranasal vaccines.[22]

The variability in mucosal immune response introduces the level of complexity in assessing the vaccine's efficacy and safety as immune responses differ significantly from systemic immunity generated by injectable vaccines.[3]

These challenges highlight the necessity of pharmacovigilance strategies specific to intranasal vaccines, involving enhanced monitoring of mucosal, neurological and respiratory adverse events, as well as efficient reporting systems capable of detecting the safety concerns associated with the mode of administration.[3,12]

Beyond reactogenicity and respiratory concerns, the anatomical proximity of nasal cavity to central nervous system through the olfactory epithelium raises neurological concerns specific to intranasal route that current pharmacovigilance frameworks are ill-equipped to detect.[27]

None of the four regulatory agencies - CDSCO, USFDA, EMA, ANVISA - currently mandate prospective neurologic signal monitoring as a standard requirement for intranasal vaccines, representing a critical oversight that needs to be considered by the regulatory authorities.[7,16,17,22]

CONCLUSION

Intranasal vaccines provide a promising alternative to conventional vaccine delivery, as they can produce mucosal as well as systemic immunity. However, the pharmacovigilance profile of intranasal vaccines must be improved, as indicated by the study, which points to the variations in pharmacovigilance approaches of CDSCO, USFDA, EMA, ANVISA, especially in the reporting system, surveillance and experience of the regulators. The US and EU have more advanced pharmacovigilance approaches, while India is improving its pharmacovigilance, while Brazil has no experience in pharmacovigilance for intranasal vaccines, as no vaccines is approved in the country for intranasal delivery. The study points to the urgent need for a global pharmacovigilance approach to ensure the safe use of intranasal vaccines.

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ABBREVIATIONS

ADR: Adverse Drug Reaction; **VAERS:** Vaccine Adverse Event Reporting System; **WHO:** World Health Organization; **ANVISA:** Agência Nacional de Vigilância Sanitária; **CDSCO:** Central Drugs Standard Control Organization; **EMA:** European Medicines Agency; **EU:** European Union; **USFDA:** United States Food and Drug Administration; **PV:** Pharmacovigilance; **ESS:** Enhanced Safety Surveillance; **ICSR:** Individual Case Safety Report; **UMC:** Uppsala Monitoring Centre; **AEPV:** Adverse Event Post Vaccination; **CTA:** Clinical Trial Application; **LAIV:** Live Attenuated Influenza Vaccine; **NDCT:** New Drug and Clinical Trials Rules; **REMS:** Risk Evaluation and Mitigation Strategy; **RMP:** Risk Management Plan; **BEST:** Biologics Effectiveness and Safety; **SIgA:** Secretory Immunoglobulin A.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

The structured narrative review evaluates the pharmacovigilance systems in India, the United States, the European Union, and Brazil. A comparative analysis of regulatory systems revealed significant differences in adverse event reporting, signal detection, risk management planning, database integration and data transparency. Though both the USFDA and EMA have relatively developed pharmacovigilance systems, challenges related to underreporting, limited digital integration, and restricted data accessibility persist in India and Brazil. The review highlights the need for strengthened surveillance strategies and greater international harmonization to effectively monitor the unique safety concerns associated with intranasal vaccines.

REFERENCES

1. Rakshita Salalli, Jyoti Dange, Dhiman S, Sharma T. Vaccines development in India: advances, regulation, and challenges. Clinical and Experimental Vaccine Research. 2023;12(3):193-3.
2. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children. New England Journal of Medicine. 2007;356(7):685-96.
3. Riese P, Sakthivel P, Trittel S, Guzmán CA. Intranasal formulations: promising strategy to deliver vaccines. Expert Opin Drug Deliv. 2014;11(10):1619-34.
4. U.S. Food and Drug Administration (FDA). FluMist. Silver Spring (MD): U.S. Food and Drug Administration; [updated 2024 Mar 12; cited 2025 Jul 8]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/fluMist.
5. Central Drugs Standard Control Organization (CDSCO). SmPC factsheet & PI of Incovacc (Nasal) vaccine of Ms Bharae. New Delhi: CDSCO; [cited 2025 Jul 8] Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb.
6. European Medicines Agency (EMA). Fluenz: EPAR - medicine overview. Amsterdam: European Medicines Agency. [cited 2025 Jul 8] Available from: https://www.ema.europa.eu/en/documents/overview/fluenz-epar-medicine-overview
7. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine [Internet]. 2015;33(36):4398-405.
8. Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J 2004;23(4):287-94.
9. Hoeve CE, van Haren A, Sturkenboom MCJM, Straus SMJM. Spontaneous reports of vaccination errors in the European regulatory database EudraVigilance: A descriptive study. Vaccine. 2018;36(52):7956-64.
10. Kurz X, Domergue F, Slattery J, Segec A, Szmigiel A, Hidalgo-Simon A. Safety monitoring of Influenza A/H1N1 pandemic vaccines in EudraVigilance. Vaccine. 2011;29(26):4378-87.
11. Carvalho M, Duarte I, Nunes R. Pharmacovigilance in Brazil: The Government Monitoring of Adverse Events Reported from COVID-19 Vaccine-A Narrative Review. Healthcare [Internet].12(3):371-1
12. Hodel KVS, Fiuza BSD, Conceição RS, Aleluia ACM, Pitanga TN, Fonseca LM dos S, *et al.* Pharmacovigilance in Vaccines: Importance, Main Aspects, Perspectives, and Challenges-A Narrative Review. Pharmaceuticals. 2024.1;17(6):807-23.
13. Hans M, Gupta SK. Comparative evaluation of pharmacovigilance regulation of the United States, United Kingdom, Canada, India and the need for global harmonized practices. Perspectives in Clinical Research. 2018;9(4):170-4.
14. ANVISA. Páginainicial. Agência Nacional de *Vigilância sanitária* - Anvisa. Available from: https://www.gov.br/anvisa/pt-br
15. Wong JC, Lao CT, Yousif MM, Luga JM. Fast Tracking-Vaccine Safety, Efficacy, and Lessons Learned: A Narrative Review. Vaccines. 2022;10(8):1256
16. Leal MM, Sanz MM, Ferrando JRC, Martinez-Martinez F. A comparative analysis of the pharmacovigilance systems of Brazil, Spain, the European Union and the United States based on the information provided by their regulatory agency websites. DARU Journal of Pharmaceutical Sciences. 2019;27(1):379-87.
17. Draft regulatory guidelines for development of vaccines with special consideration for COVID-19 vaccine central drugs Standard Control Organization Directorate General of Health Services Ministry of Health and Family Welfare Government of India [Internet]. Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadPublic_NoticesFiles/Regulatory_guidelines_for__development_of_Vaccine_20.9.20.pdf
18. Clinical Research Regulation for Brazil | ClinRegs [Internet]. clinregs.niaid.nih.gov. Available from: https://clinregs.niaid.nih.gov/country/brazil
19. CDC. Live Attenuated Influenza Vaccine [LAIV] (The Nasal Spray Flu Vaccine) [Internet]. Influenza (Flu). 2024. Available from: https://www.cdc.gov/flu/vaccine-types/nasalspray.html
20. Izurieta HS. Adverse Events Reported Following Live, Cold-Adapted, Intranasal Influenza Vaccine. JAMA. 2005;294(21):2720.
21. US Food and Drug Administration. Package Insert - FluMist Quadrivalent (Influenza Vaccine Live, Intranasal). Silver Spring, MD: US FDA; 2024. Available from: https://www.fda.gov/files/Package-Insert-FluMist-Quadrivalent.pdf
22. McNaughton R, Lynn E, Osborne V, Coughtrie A, Layton D, Shakir S. Safety of Intranasal Quadrivalent Live Attenuated Influenza Vaccine (QLAIV) in Children and Adolescents: A Pilot Prospective Cohort Study in England. Drug Safety. 2016;39:323-33
23. Singh C, Verma S, Reddy P, Diamond MS, Curiel DT, Patel C, *et al.* Phase III Pivotal comparative clinical trial of intranasal (iNCOVACC) and intramuscular COVID-19 vaccine (Covaxin®). npj Vaccines. 2023;8(1):1-9.
24. Meher B. Vaccine pharmacovigilance in India: Current context and future perspective. Indian Journal of Pharmacology. 2019;51(4):243.
25. Micallef B, Jean-Michel Dogné, Sultana J, Sabine, Nisticò R, Serracino-Inglott A, *et al.* An Exploratory Study of the Impact of COVID-19 Vaccine Spontaneous Reporting on Masking Signal Detection in EudraVigilance. Drug safety. 2023;46(11):1089-103.
26. Li J, Wu G, Huang Z, Hu J, Tie X, Wu H, *et al.* Advances and prospects of respiratory mucosal vaccines: mechanisms, technologies, and clinical applications. npj Vaccines. 2025;10(1).

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