Test file: Real-World Safety Profile of Microneedle-Array Influenza Vaccines: A Pharmacovigilance Study

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Abstract

Background: While clinical trials have demonstrated the safety of microneedle array (MNA) influenza vaccines, real-world evidence remains limited. This study aimed to characterize the post-marketing safety profile of MNA influenza vaccines using spontaneous adverse event reporting system data.

This large-scale pharmacovigilance study demonstrates that MNA influenza vaccines have a favorable safety profile in real-world use, characterized by predominantly mild, local application site reactions and fewer systemic adverse events compared to conventional influenza vaccines. These findings support the continued use and monitoring of MNA vaccine platforms.

Keywords: Microneedle Array; Influenza Vaccine; Pharmacovigilance; Vaccine Safety; Real-World Evidence; Adverse Events

1. Introduction

Influenza remains a significant global public health concern, causing substantial morbidity and mortality annually [1]. The introduction of microneedle array (MNA) technology for influenza vaccination represents a major advancement in vaccine delivery systems, offering potential benefits including improved stability, reduced need for cold chain storage, and possible self-administration [2]. While randomized clinical trials have established the efficacy and short-term safety of MNA influenza vaccines [3,4], the comprehensive safety profile in real-world clinical practice requires further investigation.

Clinical trials, though essential for initial safety assessment, are limited by their relatively small sample sizes, selective populations, and short follow-up durations [5]. Post-marketing surveillance through spontaneous reporting systems provides valuable complementary data by capturing adverse events (AEs) across diverse populations and practice settings, enabling detection of rare or unexpected safety signals [6]. The FDA Adverse Event Reporting System (FAERS) and WHO Vigibase are among the largest such databases, containing millions of reports that can be analyzed to characterize drug and vaccine safety profiles [7].

Previous analyses of MNA vaccine safety have primarily focused on data from controlled clinical trials [8,9]. However, as MNA influenza vaccines have entered wider clinical use, systematic evaluation of real-world safety data becomes imperative. This study aims to fill this evidence gap by conducting a comprehensive pharmacovigilance analysis of MNA influenza vaccines using data from major international spontaneous reporting systems.

2. Methods

2.1 Data Sources and Study Period

We conducted a retrospective analysis of spontaneous adverse event reports from two primary databases: the FDA Adverse Event Reporting System (FAERS) and the WHO Global Individual Case Safety Reports database (Vigibase). The study period spanned from January 1, 2018, to December 31, 2023, covering the initial post-approval period for MNA influenza vaccines. FAERS data were obtained through the FDA's public dashboard, while Vigibase data were accessed through the WHO Uppsala Monitoring Centre.

2.2 Case Identification and Processing

Reports involving MNA influenza vaccines were identified using standardized vaccine names and product codes. Conventional influenza vaccines were identified using established methodology from previous pharmacovigilance studies [10]. Duplicate reports were identified and removed using the recommended FDA method based on case number, patient demographics, and event date [11].

The Medical Dictionary for Regulatory Activities (MedDRA version 26.0) was used to code adverse events. Events were analyzed at the Preferred Term (PT) level. Serious adverse events were defined according to FDA criteria as events resulting in death, hospitalization, disability, or requiring intervention to prevent permanent impairment [12].

2.3 Statistical Analysis

Descriptive statistics were used to characterize the study population and adverse event reports. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using medians and interquartile ranges (IQR). Disproportionality analysis was performed using reporting odds ratios (ROR) with 95% confidence intervals [13]. A signal was considered potential when the lower limit of the 95% CI exceeded 1.0 and there were at least 3 cases reported [14].

Time-to-onset analysis was conducted for reports that included both vaccination date and adverse event onset date. We compared reporting patterns between MNA vaccines and conventional influenza vaccines using chi-square tests for categorical variables and Mann-Whitney U tests for continuous variables. All analyses were performed using R version 4.3.1 and SAS version 9.4.

3. Results

3.1 Characteristics of Adverse Event Reports

During the 6-year study period, we identified 12,457 reports of adverse events involving influenza vaccines from the combined databases. Of these, 847 reports (6.8%) involved MNA influenza vaccines. The majority of reports for MNA vaccines came from the United States (68.2%), followed by Japan (15.3%) and European countries (12.1%).

Patients receiving MNA vaccines had a median age of 45 years (IQR: 32-58), with a nearly equal gender distribution (51.2% female, 48.8% male). Reports for conventional influenza vaccines involved older patients (median age: 58 years, IQR: 45-72) and had a higher proportion of female patients (58.7%). Most reports for MNA vaccines were submitted by consumers (42.3%) and healthcare professionals (38.1%), whereas conventional vaccine reports were predominantly submitted by healthcare professionals (65.2%).

3.2 Nature and Pattern of Reported Adverse Events

The majority of reports for MNA vaccines were classified as non-serious (92.3% vs 78.9% for

conventional vaccines, p<0.001). Among serious reports for MNA vaccines, the most common categories were hospitalization (4.1%) and other medically important conditions (2.8%). There were no reports of death directly attributed to MNA vaccines.

Application site reactions constituted the most frequently reported events for MNA vaccines (65.4% of reports), with erythema (38.2%), pruritus (29.5%), and swelling (22.8%) being the most common specific reactions. Systemic events such as headache (15.3%) and fatigue (12.6%) were less frequently reported compared to conventional vaccines (headache: 28.4%, fatigue: 24.7%).

3.3 Disproportionality Analysis

The disproportionality analysis revealed several significant safety signals (Table 1). MNA vaccines showed significantly higher reporting of application site reactions including erythema (ROR: 8.45, 95% CI: 7.12-10.03), pruritus (ROR: 6.78, 95% CI: 5.43-8.47), and swelling (ROR: 5.92, 95% CI: 4.85-7.23). Conversely, MNA vaccines had significantly lower reporting of systemic events including fever (ROR: 0.45, 95% CI: 0.32-0.63), myalgia (ROR: 0.52, 95% CI: 0.41-0.67), and arthralgia (ROR: 0.61, 95% CI: 0.48-0.78).

3.4 Time-to-Onset Analysis

The median time-to-onset of adverse events was significantly shorter for MNA vaccines (0 days, IQR: 0-1) compared to conventional vaccines (1 day, IQR: 0-2, p<0.001). For application site reactions specifically, 89.2% of events with MNA vaccines were reported on the same day as vaccination, compared to 45.3% for conventional vaccines. The time-to-onset distribution showed a sharp peak immediately following vaccination for MNA vaccines, with rapid decline thereafter.

4. Discussion

This comprehensive pharmacovigilance study provides important real-world evidence regarding the safety profile of MNA influenza vaccines. Our analysis of over 12,000 adverse event reports demonstrates that MNA vaccines have a distinct safety pattern characterized by increased local application site reactions but decreased systemic adverse events compared to conventional influenza vaccines.

The high frequency of application site reactions, particularly erythema and pruritus, is consistent with the known mechanism of MNA action. Microneedles create microscopic conduits in the skin, stimulating local immune responses and causing transient inflammatory reactions [15]. These reactions are generally mild and self-limiting, as evidenced by their low association with serious outcomes in our dataset. The immediate onset of these local reactions (median 0 days) further supports their direct relationship to the vaccination procedure.

The significantly reduced reporting of systemic adverse events such as fever, myalgia, and arthralgia with MNA vaccines represents a notable finding. This may be attributed to several factors, including the intradermal delivery route which has been associated with different immunogenicity patterns [16], and potentially lower systemic exposure to vaccine components or immune activators. This improved systemic tolerability could enhance vaccine acceptability, particularly among individuals who have experienced significant systemic reactions to conventional vaccines.

4.1 Limitations

Our study has several limitations inherent to spontaneous reporting system analyses. Underreporting is a well-known limitation, and reporting patterns may be influenced by increased vigilance for new vaccine technologies. The data quality depends on accurate and complete

reporting by healthcare professionals and consumers. Additionally, we cannot calculate incidence rates or establish causal relationships due to the lack of denominator data and controlled comparison groups.

5. Conclusion

This large-scale pharmacovigilance analysis demonstrates that MNA influenza vaccines have a favorable and distinct safety profile in real-world clinical practice. The predominance of mild, local application site reactions and reduced systemic adverse events supports the continued use and monitoring of this innovative vaccine platform. Ongoing surveillance and further studies with active comparator groups are warranted to fully characterize the long-term safety profile of MNA vaccines.

References

[1] Iuliano AD, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018;391(10127):1285-1300.

[2] Prausnitz MR. Engineering microneedle patches for vaccination and drug delivery to skin. Annu Rev Chem Biomol Eng. 2017;8:177-200.

[3] Rouphael NG, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch: a randomised trial. Lancet. 2017;390(10095):649-658.

[4] Levin Y, et al. A phase 1/2 randomized study of a novel microneedle array-based influenza vaccine. Vaccine. 2022;40(15):2274-2281.

[5] Polack FP, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603-2615.

[6] Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J. 2008;42(5):409-419.

[7] Moore TJ, et al. Reported adverse drug events in infants and children under 2 years of age. Pediatrics. 2002;110(5):e53.

[8] Marshall S, et al. Safety and immunogenicity of a microneedle patch for influenza vaccination in healthy adults: A phase 1 trial. Vaccine. 2021;39(17):2381-2388.

[9] Edens C, et al. A microneedle patch containing measles vaccine is immunogenic in non-human primates. Vaccine. 2015;33(37):4711-4718.

[10] Yamasaki Y, et al. Analysis of vaccine-related adverse events reported to the US Vaccine Adverse Event Reporting System. Clin Infect Dis. 2022;75(1):e752-e760.

[11] FDA. Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data. 2021.

[12] FDA. Code of Federal Regulations Title 21. 2023.

[13] Rothman KJ, et al. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13(8):519-523.

[14] Bate A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315-321.

[15] Kim YC, et al. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547-1568.

[16] Laurent PE, et al. Evaluation of the clinical performance of a new intradermal vaccine administration technique and associated delivery system. Vaccine. 2007;25(52):8833-8842.