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Opinion

The Association between Vaccine Factory-Release Conditions and Adverse Events Following Immunization: A Retrospective Analysis

Huang Juan[1], Zhu Zhenggang[1]* and Song Yanchao[2]*

[1]Wuhan Center for Disease Control and Prevention, China

[2]Huangshi Center for Disease Control and Prevention, China

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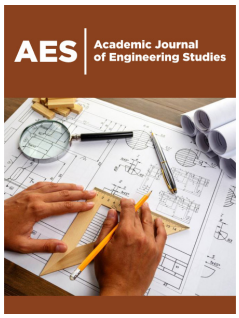

***Corresponding authors:** Zhu Zhenggang, Wuhan Center for Disease Control and Prevention, Hubei, China
Song Yanchao, Huangshi Center for Disease Control and Prevention, Hubei, China

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Introduction

Vaccination is one of the most cost-effective and successful public health interventions. It not only prevents infectious diseases caused by pathogens such as bacteria and viruses but also helps curb their transmission by establishing herd immunity [1]. However, with the rapid expansion of vaccine production capacity and the increasing diversity of vaccine types, public concern over Adverse Events Following Immunization (AEFI) has risen significantly in recent years. While the benefits of vaccination undeniably outweigh the risks, the recurrence of AEFI has led to heightened caution-sometimes even among healthcare decision-makers, who may exhibit greater hesitancy than vaccine recipients themselves [2]. How to objectively and fairly evaluate vaccine safety is crucial in addressing vaccine hesitancy and ensuring the smooth implementation of immunization programs.

Many countries have established surveillance systems to monitor the occurrence of post-vaccinated AEFI, though surveillance methods may vary across regions. In China, the national AEFI surveillance system was formally established in 2008, with subsequent enhancements in 2015 and 2018 [3]. All AEFI cases are collected through designated reporting units, including vaccination sites, medical institutions, disease control and prevention agencies, drug adverse reaction monitoring centers, vaccine manufacturers, and vaccine distributors. Additionally, if vaccine recipients or their guardians identify any adverse physical symptoms, they may voluntarily report the specific details sought to the healthcare providers at the vaccination site. According to their etiology, AEFIs are classified into five categories, such as common vaccine reactions, adverse vaccine reactions, coincidental events, psychogenic reactions, vaccine quality-related incidents or immunization errors. By severity, cases are further stratified as non-serious AEFI or serious AEFI [4]. All reporting and diagnostic criteria align with the functional assessment requirements of the National Regulatory Authority (NRA) for vaccines.

Previous studies on post-marketing AEFI mainly focused on comparing the differences in the reported incidence rates of AEFI across different types of vaccines based on the demographic characteristics, clinical diagnoses, disease symptoms, and the number of vaccine doses. For instance, Liu Jie-chen et al. [5] examined AEFI reports from Shanghai between 2011-2015 following administration of 5042737 doses of DTaP (Diphtheria,

Tetanus, acellular Pertussis) -containing vaccines, including: 4315271 doses of DTaP, 100377 doses of DTaP-Hib (Haemophilus influenzae type b), and 627089 doses of DTaP-Hib-IPV (Inactivated poliovirus vaccine). The overall AEFI incidence rate was 457.45 per 100000 doses. DTaP-Hib-IPV demonstrated the common reaction incidence of 1009.59 / 100000 doses (n = 6331), compared to 362.63 / 100000 (n = 364) for DTaP-Hib and 369.34 / 100000 (n = 15938) for DTaP. There were significant differences between DTaP and DTaP-Hib-IPV ($\chi^2 = 5003.704, P < 0.001$), as well as between DTaP-Hib and DTaP-Hib-IPV ($\chi^2 = 397.167, P < 0.001$). In contrast, no significant difference was observed between DTaP and DTaP-Hib ($\chi^2 = 0.120, P = 0.729$). Additionally, among the 404 adverse reaction reports, there were 322 cases from DTaP (7.46 / 100000 doses), 7 cases from DTaP-Hib (6.97 / 100000 doses), and 75 cases from DTaP-Hib-IPV (11.96 / 100000 doses). Based on the data provided in this literature, our differential analysis similarly revealed no significant difference in adverse reaction reporting rates between DTaP and DTaP-Hib vaccines ($\chi^2 = 0.031, P = 0.859$), but DTaP-Hib-IPV showed a significantly higher reporting rate compared to DTaP alone ($\chi^2 = 13.793, P < 0.001$). Notably, we found no statistically significant difference between DTaP-Hib and DTaP-Hib-IPV ($\chi^2 = 1.909, P = 0.167$). Allergic rash, the most frequently reported adverse reaction, occurring at rates of 7.11 per 100000 doses for DTaP (307 cases), 6.97 per 100000 doses for DTaP-Hib (7 cases), and 11.48 per 100000 doses for DTaP-Hib-IPV (72 cases). There was no statistically significant difference between DTAP and DTaP-Hib ($\chi^2 = 0.003, P = 0.958$), nor between DTaP-Hib and DTaP-Hib-IPV ($\chi^2 = 1.619, P = 0.203$), however, the reported incidence rate of DTaP-Hib-IPV was significantly higher than that of DTAP ($\chi^2 = 13.620, P < 0.001$). In this study, the observed differences were attributed to factors such as vaccine component complexity, cost variations, and parental vigilance levels [5].

Nevertheless, most current research on vaccine-related AEFI whether through post-marketing surveillance or clinical trials, they primarily focused on basic analyses of AEFI monitoring reports or experimental outcomes [6-9]. These studies have not sufficiently investigated potential underlying causes of AEFI, particularly factors related to vaccine manufacturing conditions prior to distribution. To address this gap, we conducted a comparative analysis of 18 randomly selected final product quality test reports for DTaP and DTaP-Hib-IPV vaccines during 2016-2025. Our findings found significant differences in two key physicochemical parameters: the pH values in DTaP-Hib-IPV were significantly higher than that in DTaP (t = -15.244, P < 0.001), with the mean pH of DTaP was 6.525 (SD = 0.148), and DTaP-Hib-IPV was 7.517 (SD = 0.075). The osmolality values also have significances between the two vaccines (t = -40.300, P < 0.001), with DTaP measuring 271.583 ± 6.815 mOsm/kg compared to 482.333 ± 15.744 mOsm/kg for DTaP-Hib-IPV. The remaining tested parameters (thimerosal, glutaraldehyde, and free formaldehyde) showed qualitatively comparable profiles between these vaccines, with no substantial quantitative differences observed.

The Point Worth Discussing Are

1. Will an increase in pH value raise the probability of common reactions such as skin itching, redness, swelling, and induration? Under normal circumstances the skin surface or stratum corneum has a pH of 4-6. This weakly acidic environment was deemed to regulate microbial balance and prevents infections. When skin is damaged, the subcutaneous tissue has a physiological pH of 7.4. Most pathogenic microbes thrive in environments with a pH above 6, and a higher pH may not only aid epithelial cell growth but also foster conditions more susceptible to microbial infections [10]. Randomly sampled factory quality reports for DTap-containing vaccines in our study show their pH ranges from 6.1 to 7.4, and as pH levels rise, the incidence of common reactions may increase accordingly.

2. Will high osmolality increase common reactions, inflammatory reactions, and allergic reactions at the injection site? The normal osmolality range for maintaining cell volume stability and extracellular fluid equilibrium is 275-295mOsm/kg. Under hypotonic conditions, cells swell due to water gaining, whereas hypertonicity leads to cellular shrinkage via water loss. Clinically significant hyperosmolarity is defined when serum osmolality exceeds 320mOsm/kg, a condition driven by osmosis-the movement of water across a semipermeable membrane from regions of lower solute concentration to higher concentration [11,12]. At the injection site, high osmolarity induces cell shrinkage and tissue fluid exudation, creating a pro-inflammatory microenvironment that may provoke localized inflammatory reactions, and further potentially eliciting systemic immune responses, for example, allergic reactions in some susceptible vaccine recipients.

3. Will the cumulative effect of high pH value and high osmolality correspondingly enhance the occurrence of inflammatory reactions and allergic reactions at the vaccination site? Allergic rash is essentially an allergic reaction, representing the immune system's response to a range of inflammatory stimuli and antigenic substances [13]. An elevated pH value promotes microbial growth and epithelial cell proliferation, which can simultaneously trigger redness, swelling, and induration at the vaccination site. When combined with high osmolality-a factor that may also induce similar inflammatory reactions at the injection site, this cumulative may affect intensify the immune response in some vaccine recipients, further exacerbating their allergic reactions, such as increasing the risk of allergic rash development.

The above conclusions are mainly based on retrospective analyses of previous data and literature. We anticipate that future clinical trials of vaccines/pharmaceuticals, post-marketing safety surveillance studies, and the establishment of quality control standards will place greater emphasis on investigating the correlation between product components and AEFI. Furthermore,

we advocate for more experimental data to validate how specific parameters-particularly pH and hyperosmolality influence physiological responses and induce systemic changes following drug administration or vaccination.

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