



Analysis of Adverse Events Associated with Chlorhexidine Using the U.S. Food and Drug Administration Adverse Event Reporting System Data

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ABSTRACT

Objectives: Chlorhexidine, a key component of periodontal treatments and preventive dentistry, can occasionally cause various side effects. This study aims to compare the adverse effects of chlorhexidine used in dental applications, analyzing them by demographic factors and severity, as reported in the Food and Drug Administration Adverse Event Reporting System.

Materials and Methods: Dental adverse event reports related to the use of chlorhexidine for dental and/or oral reasons, from the Food and Drug Administration Adverse Event Reporting System database, were retrospectively analyzed from the reporting start date to December 2025. Adverse effects were categorized based on the patients' demographic and clinical characteristics and compared according to their severity.

Results: A search of the database using the keywords "chlorhexidine" and "chlorhexidine gluconate" related to dental and oral indications between 1977 and 2025 identified a total of 651 cases. Of these, 407 cases (62.5%) were classified as serious, and 18 deaths have been reported. Among the cases, 66.4% involved females, 26.3% involved males, and gender information was not reported for 7.4%. Regarding age distribution, most cases (46.4%) occurred in individuals aged 18–64 years. Of these cases, 37.6% reported only systemic adverse effects, 45.9% reported only dental/oral adverse effects, and 16.4% reported both systemic and oral adverse effects. Among dental/oral adverse events, tooth discoloration, dry mouth, and gingival pain were the most frequently reported, while the highest Reporting Odds Ratio (ROR) value was observed in taste disorder (ROR: 378.7).

Conclusions: The data reveal that a significant proportion of adverse events reported from chlorhexidine use for dental and/or oral purposes involved mucosal, periodontal and inflammatory reactions. While serious consequences were linked to the use of additional medications, it is important to emphasize that 18 fatalities were reported. Integrating clinical evidence with pharmacovigilance data has the potential to influence clinicians' prescribing preferences for chlorhexidine in dental practice, facilitating more informed and evidence-based decision-making.

Keywords: Chlorhexidine, chlorhexidine gluconate, pharmacovigilance, tooth discoloration, United States Food and Drug Administration

Klorheksidin ile İlişkili Olumsuz Olayların ABD Gıda ve İlaç İdaresi Olumsuz Olay Bildirim Sistemi Verileri Kullanılarak Analizi

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ÖZ

Amaç: Periodontal tedavilerin ve önleyici diş hekimliği uygulamalarının ayrılmaz parçası olan klorheksidin zaman zaman çeşitli yan etkilere yol açabilir. Bu çalışmanın amacı ABD Gıda ve İlaç Dairesi Advers Olayları Raporlama Sistemi'nde diş hekimliği nedenleriyle kullanılan klorheksidin advers etkilerini demografik olarak ve şiddetine göre karşılaştırmaktır.

Gereç ve Yöntemler: Gıda ve İlaç Dairesi Advers Olayları Raporlama Sistemi veri tabanında dental ve/veya oral sebeplerle klorheksidin kullanımına ilişkin dental advers olay raporları, raporlama başlangıcından Aralık 2025'e kadar retrospektif olarak analiz edildi. Advers etkileri hastaların demografik ve klinik özelliklerine göre tanımlandı ve şiddetlerine göre karşılaştırıldı.

Bulgular: Veri tabanında 1977–2025 yılları arasında dental ve oral endikasyonlarla ilişkili kullanılan "chlorhexidine" ve "chlorhexidine gluconate" anahtar kelimeleriyle yapılan taramada, toplam 651 olgu tanımlanmıştır. Bu olguların 407'si (%62,5) ciddi olarak sınıflandırılmış, 18 adet ölüm vakası bildirilmiştir. Vakaların %66,4'ü kadın, %26,3'ü erkek olup %7,4'ünde cinsiyet bilgisi bildirilmemiştir. Olguların büyük çoğunluğu klorheksidin glukonat (%85,6) kullanımına bağlıdır. Yaş dağılımı incelendiğinde vakaların çoğunun 18–64 yaş aralığında olduğu (%46,4) görülmüştür. Bu vakaların %37,6'sı yalnızca sistemik, %45,9'u yalnızca dental/oral, %16,4'ü ise hem sistemik hem oral advers etki bildirmiştir. Dental/oral advers olaylar arasında en sık diş renklenmesi, ağız kuruluğu ve gingival ağrı bildirilirken, en yüksek Raporlama Olasılık Oranı (ROO) değeri tat bozukluğunda (ROO: 378,7) saptanmıştır.

Sonuçlar: Veriler, dental ve/veya oral sebeplerle klorheksidin kullanımına bağlı bildirilen advers olayların önemli bir bölümünde inflamatuvar, mukozal ve periodontal reaksiyonların ortaya çıktığını ortaya koymaktadır. Ciddi sonuçlar ek ilaç kullanımının bildirildiği durumlarla ilişkili olmakla birlikte, 18 ölüm vakasının olduğu vurgulanmalıdır. Klinik kanıtların farmakovijilans verileriyle bütünleştirilmesi, klinisyenlerin diş hekimliği uygulamalarında klorheksidin reçete etme tercihlerini etkileme potansiyeline sahiptir ve daha bilgilili ve kanıta dayalı karar almaya olanak tanır.

Anahtar Kelimeler: Amerika Birleşik Devletleri Gıda ve İlaç Dairesi, diş renklenmesi, farmakovijilans, klorheksidin, klorheksidin glukonat

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Introduction

Chlorhexidine (CHX) is a cationic pharmacological agent with potent antiplaque and antimicrobial properties, widely used following various dental treatments and for prophylactic purposes in high-risk patient groups.¹ It exerts its antimicrobial effect primarily by binding to the negatively charged surfaces of gram-positive bacteria, thereby disrupting their cell membrane structure.¹ Additionally, CHX extends its antimicrobial efficacy by binding to the pellicle layer on oral surfaces, allowing for its slow release over time.^{2,3} CHX has low acute oral toxicity and it is minimally absorbed from the gastrointestinal tract.⁴ Although it is not among the systemically administered oral drugs, it can cause some local side effects such as discoloration of the teeth and restorations, altered taste perception, and irritation of the oral mucosa.⁵ These potential adverse reactions are a significant concern for dentists, other healthcare professionals, and patients, often occurring during or immediately after use. These reactions can range from mild to severe, depending on the chemical structure of CHX and individual patient factors and may manifest across a wide spectrum from predictable effects to unexpected side effects.⁶

A large proportion of dental procedures are performed in out-of-hospital clinical settings. This underscores the importance of determining whether the use of CHX in clinical practice causes serious adverse events, identifying which adverse events are most frequently associated with it, and understanding the relationships between these reactions and the demographic and clinical characteristics of patients. Furthermore, the prescription of CHX for home use following dental treatments further increases the clinical significance of this issue.

The first step toward ensuring patient safety in dental care is the identification of adverse events associated with dental treatments.⁷ Because there is no comprehensive and centralized source for identifying the causes of drug side effects and systematically monitoring them, literature reviews and the examination of self-reported adverse event systems have become essential tools.⁸ The U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) is a widely used and important database for monitoring post-marketing drug safety.⁸ FAERS encompasses voluntary reports of adverse events, medication errors, and product quality issues for approved drugs submitted by healthcare practitioners, patients, and pharmaceutical manufacturers, and serves as a key pharmacovigilance tool for post-marketing drug safety monitoring.⁹ Although several case reports, clinical and observational studies have reported CHX-related adverse events in dental practice,^{5,6} evidence derived from large-scale pharmacovigilance databases remains scarce, and systematic evaluations distinguishing the severity of reported events are particularly limited.¹⁰

Therefore, we hypothesized that chlorhexidine use is associated with a disproportionate reporting of both serious and non-serious adverse events compared with

other medications in the FAERS database. This study aimed to systematically evaluate and compare serious and non-serious adverse events associated with chlorhexidine use in dental practice using the FAERS database, in order to characterize potential risk profiles, enhance clinical awareness to improve patient safety and address existing gaps in population-level safety evidence relevant to dental patients.

Materials and Methods

This cross-sectional study was conducted as a retrospective analysis of adverse event reports related to the dental use of CHX, obtained from the FAERS. The FAERS database is publicly accessible and contains anonymized data; therefore, ethical approval was not required for this study. All procedures were carried out in accordance with the STROBE reporting guidelines.

Data collection

Within the FAERS database, adverse events are classified in order to enable standardized evaluation of heterogeneous reports submitted for pharmacovigilance purposes. These classifications encompass a range of outcomes, including death, life-threatening conditions, hospitalization, disability, congenital anomalies, and events necessitating medical intervention. In addition, they also include non-serious and other less clinically significant events. The analysis encompassed reports pertaining to CHX and CHG formulations that are frequently employed in clinical practice. In order to identify reports relevant to dental applications, the indication fields for each product were subjected to careful review. This evaluation was independently performed by an experienced periodontist (S.A.), a pedodontist (A.K.), and a pharmacologist (B.S.), followed by a consensus discussion to resolve discrepancies. The process of data extraction from the FAERS database was concluded on 15 December 2025.

Study Variables

The principal objective of the study was to classify adverse events as either serious or not serious in line with the criteria set out in the FAERS reporting guidelines. The occurrence of death, hospitalization, life-threatening events, disability, and congenital anomalies were analyzed as serious adverse events. Furthermore, a comprehensive analysis of adverse events by gender and age group of registered data subjects, concomitant medication use, and type of reporting was undertaken as supplementary outcomes. The patient age demographic was divided into four distinct groups: '<18 years', '18–44 years', '45–65 years', and '>65 years'. Gender was divided into three groups: unknown, female, and male.

Statistical Analysis

All data were extracted from the Food and Drug Administration Adverse Event Reporting System (FAERS) database and analyzed descriptively. Adverse events associated with chlorhexidine use for dental and/or oral indications were summarized according to demographic variables (age, sex), clinical characteristics, and

seriousness classification (serious vs. non-serious). Categorical variables were presented as frequencies and percentages. The severity of side effects, additional medications used, and priority registration status were evaluated according to age and gender using the Kruskal-Wallis test. Pairwise comparisons were performed using the Mann-Whitney U test with Bonferroni-adjusted p values. A p-value < 0.05 was considered statistically significant. Associations between chlorhexidine exposure and reported adverse event outcomes were evaluated using reporting odds ratios (ROR) with 95% confidence intervals (CIs). Odds ratios were calculated from 2x2 contingency tables based on the presence or absence of chlorhexidine exposure and the outcome of interest with 95% confidence intervals. Statistical analyses were conducted using SPSS v23 (IBM Corp.,USA) statistical software.

Results

A search of the FAERS database using the keywords “chlorhexidine” and “chlorhexidine gluconate” identified a total of 10,704 adverse event reports submitted

between 1977 and December 15, 2025. Among these, 8,823 reports were classified as serious, and 2,827 resulted in death. Notably, 62.7% (n = 6,713) of all reports were submitted between 2020 and 2025 (Figures 1 and 2). To focus the analysis on dental-related use, records containing the terms dental, gingival, oral, periodontal, peri-implantitis, peri-coronitis, periodontitis, tooth, and teeth were selected, yielding 669 cases. Of these, 465 were domestic reports and 204 were foreign reports. After further evaluation of product names and indications for use, 18 cases related to non-oral indications (e.g., use as a wound antiseptic) were excluded. Consequently, 651 cases associated with mouthwash or local oral use of CHX or CHG were included in the final analysis. The form of 53.6% of the products used is unknown, while 17.7% are local use products in chip form, and the remaining products (28.7%) are in mouthwash form. According to the reason for use, 25.5% used CHX or CHG due to gingivitis and/or gingival bleeding, 20.3% due to periodontitis and /or periodontal diseases, and 9.1% due to dental operations. Among these, 33.9% (n = 221) were reported between 2020 and 2025.

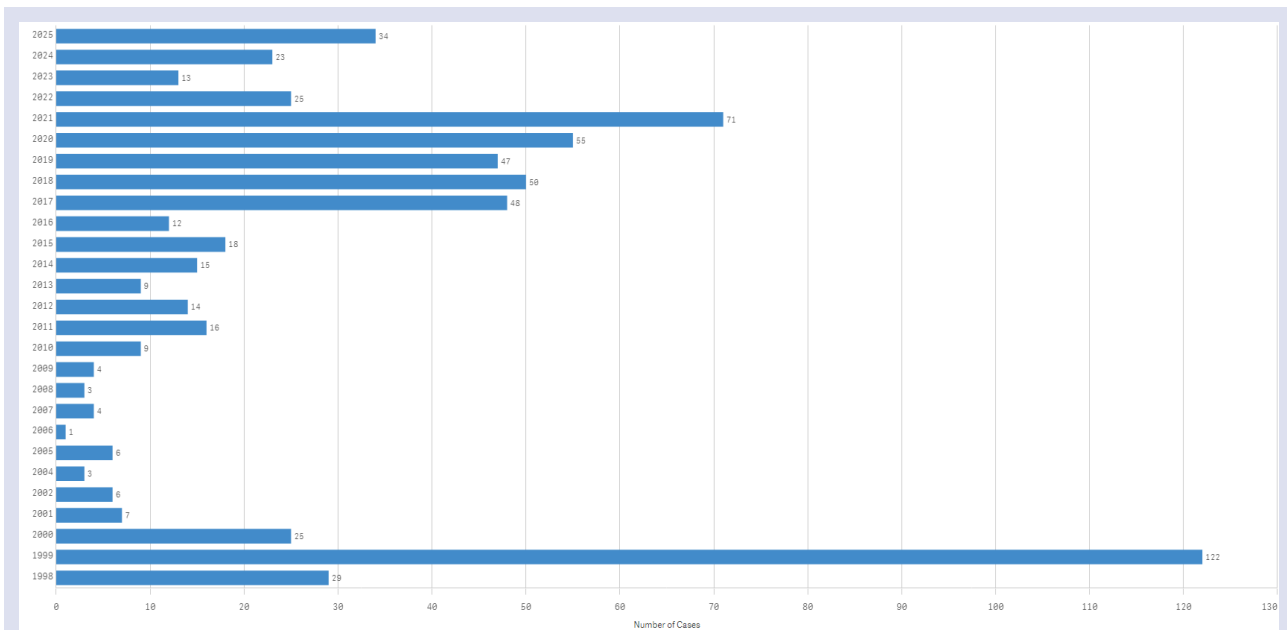


Figure 1. Annual distribution of cases identified in the FAERS database using the keywords ‘CHX’ and ‘CHG’ for dental and/or oral indications.

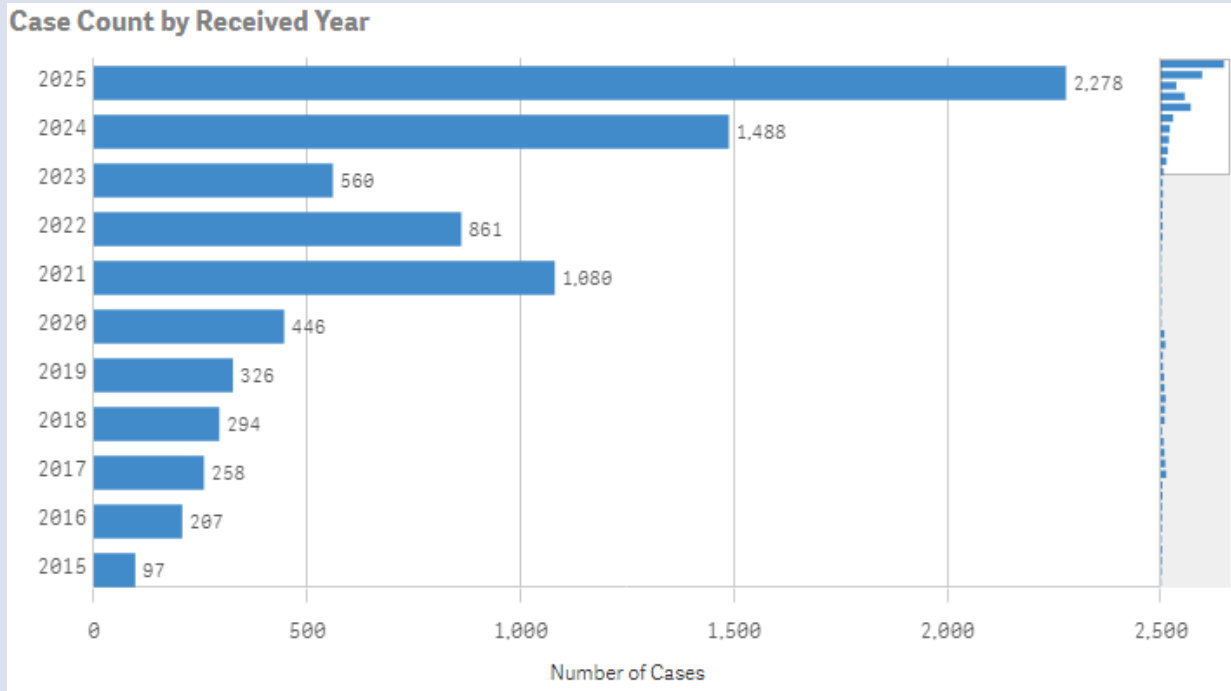


Figure 2. Distribution of reported cases associated with 'CHX' and 'CHG' in the FAERS database from 2015 to 2025.

Of the 651 cases, 407 (62.5%) were reported as serious, and 18 deaths have been reported. Among fatal cases, four deaths occurred in 2011, one in 2013, three in 2018, four in 2019, two in 2020, and four in 2021. Regarding outcome classification excluding death, 41.2% of cases were categorized as "other outcomes," 36.3% as

non-serious, 7.8% resulted in hospitalization, 5.9% resulted in disability or congenital anomalies, 3.3% were classified as life-threatening, and 2.8% required intervention (Figures 3 and 4).

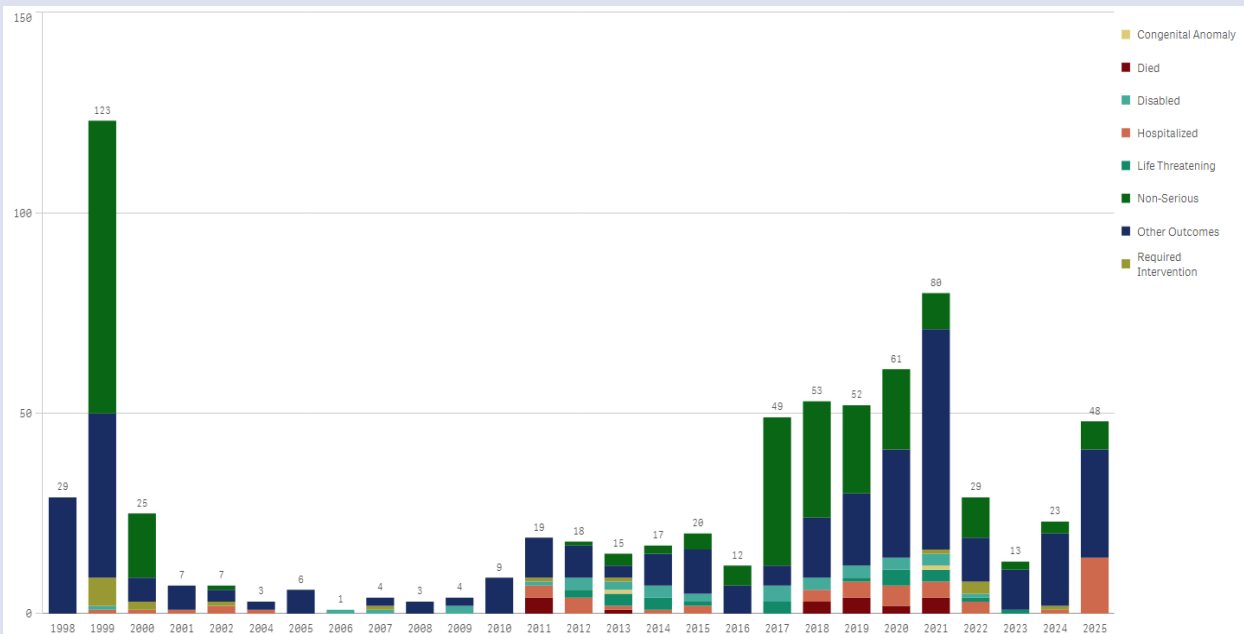


Figure 3. Annual distribution of reported adverse events in the FAERS database.

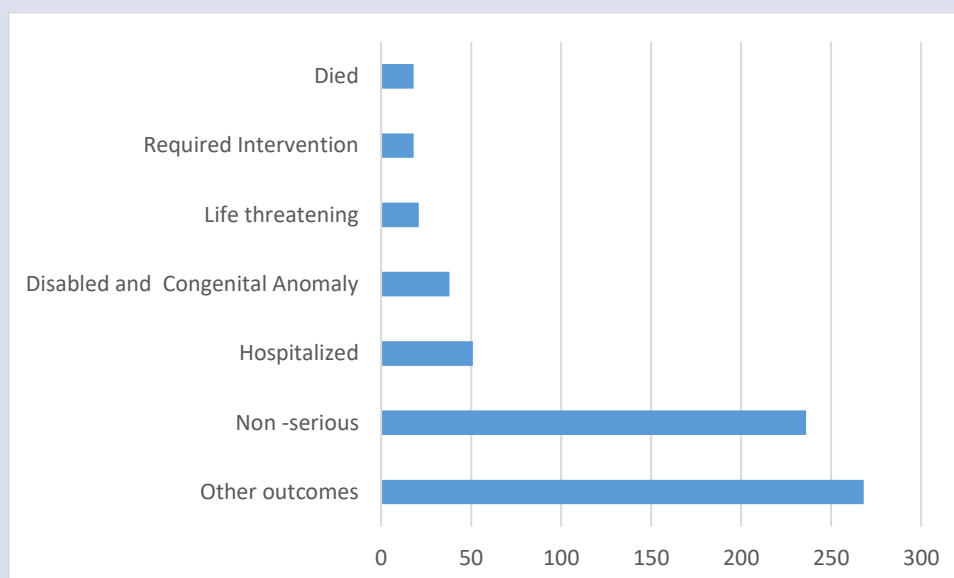


Figure 4. Distribution of adverse events by severity.

Regarding gender distribution, 432 (66.4%) were female, 171 (26.3%) were male, and 48 (7.4%) were individuals whose gender was not specified (Figure 5). In terms of the active ingredient, 85.6% (n = 557) of the cases were associated with CHG, while 14.4% (n = 94) involved products containing CHX. Age distribution showed that 4 cases (0.6%) occurred in individuals aged 12–17 years, 302 cases (46.4%) in the 18–64 year age range, 122 cases (18.7%) in individuals aged 65–84 years, and 11 cases (1.7%) in the 85 years and older age range; age information was not reported for 212 cases (32.6%) (Figure 5). Among adolescents aged 12–17 years, reported adverse events included two gastrointestinal disorders, one general disorder and administration site condition, and one respiratory, thoracic, or mediastinal disorder.

According to the type of reporter, 43.2% (n = 281) of cases were reported by consumers, 49.8% (n = 324) by healthcare professionals, and 7.1% (n = 46) by unspecified individuals. Regarding exposure patterns, 492 cases (75.6%) involved CHX or CHG alone, whereas 159 cases (24.4%) involved concomitant medication use. In terms of clinical presentation, 245 cases (37.6%) reported only systemic adverse events, 299 cases (45.9%) reported only dental or oral complaints, and 107 cases (16.4%) reported both systemic and dental/oral manifestations (Figure 6). Based on case priority classification, 223 cases (34.3%) were categorized as expedited, 283 (43.5%) as non-expedited, and 145 (22.3%) as direct reports.

The distribution of cases according to reaction groups is as follows: 301 cases involved gastrointestinal disorders, 178 general disorders and administration site conditions, 172 nervous system disorders, 132 injuries, poisoning and procedural complications, 97 infections and infestations, and others. The most frequently reported specific adverse events were premature delivery or maternal exposure during pregnancy (n = 100), dysgeusia or ageusia (n = 81), off-label use (n = 60), tooth and tongue discoloration (n = 59), gingival and oral pain (n = 57), pain (n = 43), gingivitis

(n = 36), application site reaction and pain (n = 35), dry mouth (n = 31), and taste disorder (n = 25), and others.

Among the dental and oral adverse events, the most frequently reported were tooth discoloration (n = 39), dry mouth (n = 31), gingival pain (n = 31), oral pain (n = 26), stomatitis (n = 23), toothache (n = 23), tongue discoloration (n = 20), tongue discomfort (n = 17), tongue swelling (n = 15), oral discomfort (n = 15), glossodynia (n = 15), lip swelling (n = 13), mouth ulceration (n = 10) and others.

When adverse event severity was compared according to gender, no statistically significant difference was observed (p = 0.560). Similarly, no significant difference was found between genders regarding the use of concomitant medications recorded in the database (p = 0.661).

Statistically significant differences according to gender were initially observed for active substance, age, and case priority (p < 0.001, p < 0.001, and p = 0.017, respectively); however, after Bonferroni correction for multiple comparisons, only the differences in active substance and age remained statistically significant (adjusted significance threshold p < 0.005).

Chlorhexidine gluconate was the most frequently reported active substance among females (p < 0.001). In addition, no statistically significant difference was observed in the reported age between female and male patients after Bonferroni correction (p = 0.017). In pairwise comparisons, no statistically significant difference was detected between females and males in terms of case priority (p = 0.154).

When adverse event severity was evaluated according to age groups, a statistically significant difference was observed (p < 0.001). Differences across age groups were also identified for the reported active substance and case priority (p < 0.001 for both).

After Bonferroni correction, statistically significant differences across age groups were observed only

between the 65–85 age group and the age-unknown group for case priority ($p < 0.001$). In pairwise comparisons, a significant difference in adverse event severity was observed only between the 18–64 age group and the age-unknown group ($p < 0.001$), with adverse events in the 18–64 age group being more frequently classified as non-serious.

For the reported active substance, only the comparison between the 65–85 age group and the age-unknown group remained statistically significant ($p = 0.002$). For case priority, statistically significant differences were observed between the 65–85 age group and the age-unknown group ($p < 0.001$), as well as between the 18–64 age group and the age-unknown group ($p < 0.001$). However, the difference between the 18–64 and 65–85 age groups did not remain statistically significant after adjustment ($p = 0.018$).

In the disproportionality analysis using the FAERS database, five different reporting odds ratios were

calculated for selected adverse events reported with chlorhexidine, determined by severity and clinical prevalence. Chlorhexidine exposure has been associated with anaphylactic reactions, dysgeusia, taste disorder, tooth discoloration, and maternal exposure during pregnancy and premature delivery. Calculated ROR values are presented in Table 1. The fact that ROR values were above 1 for all adverse events and 95% confidence intervals did not include 1 indicates a potential safety signal between the use of chlorhexidine and these events.

The highest ROR value was observed for taste disorder, followed by tooth discoloration and maternal exposure during pregnancy and premature delivery, respectively. The fact that $ROR > 1$ was also found for other adverse events suggests that chlorhexidine-related adverse event reports are reported disproportionately in the FAERS database compared to other drugs.

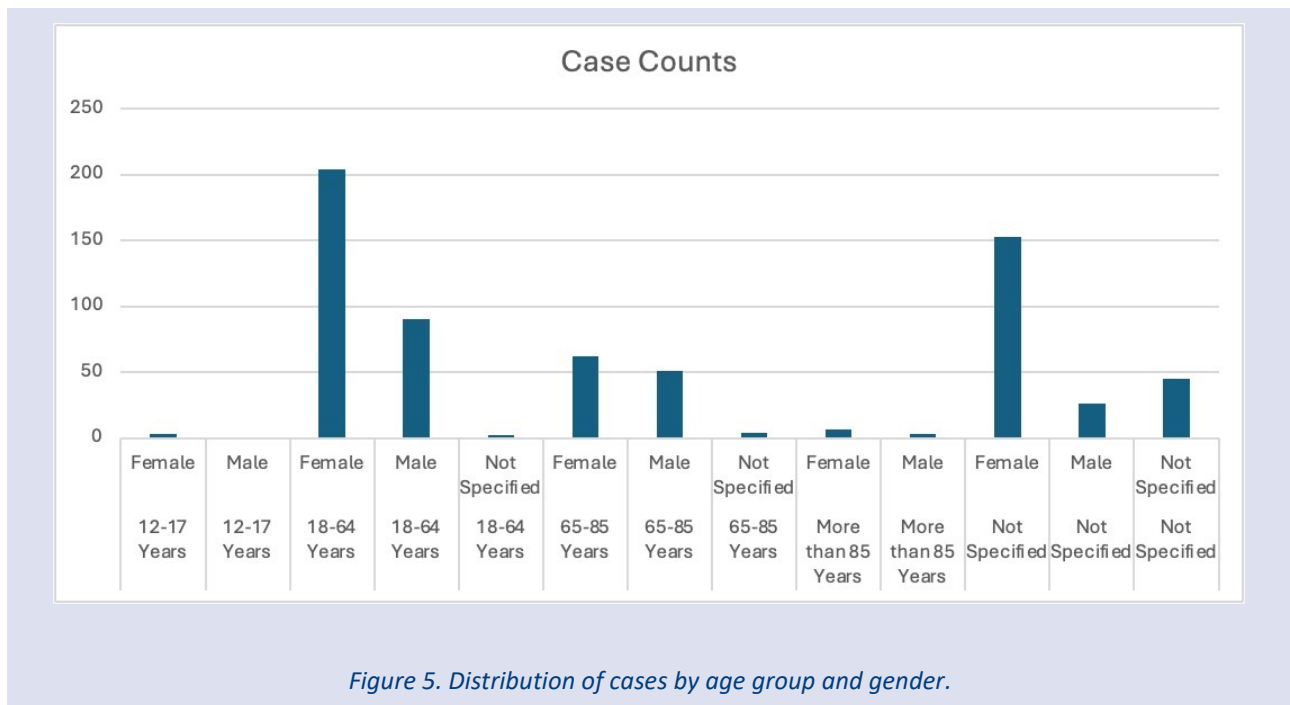


Figure 5. Distribution of cases by age group and gender.

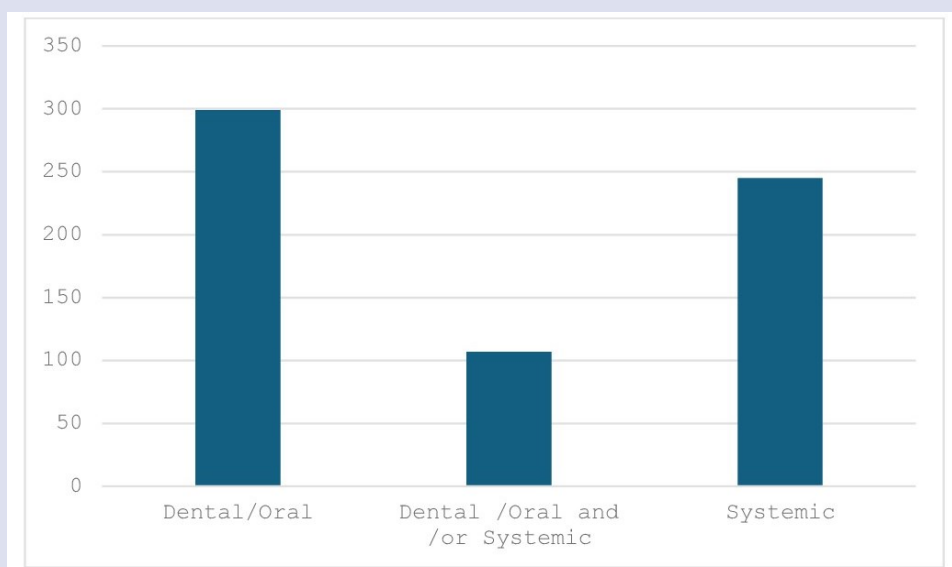


Figure 6. Distribution of adverse events by dental/oral and systemic involvement.

Table 1. Reporting odds ratios for adverse events associated with chlorhexidine use based on FAERS data

Adverse Event	ROR	95% CI
Taste Disorder	378.7	341.0 - 420.5
Tooth Discolouration	130.74	115.18 - 148.41
Maternal exposure during pregnancy and premature delivery	47.13	44.71 - 49.68
Anaphylactic reactions	17.90	16.00 - 20.03
Dysgeusia	6.50	5.55 - 7.62

Discussion

CHX is widely used in healthcare settings due to its high antimicrobial efficacy, broad clinical spectrum, and long-lasting substantivity. It is a cationic bis-biguanide agent effective against a wide range of microorganisms.³ However, frequent use of daily products can lead to allergic sensitization, and cause anaphylactic reactions in some patients. The incidence of CHX-induced anaphylaxis has been reported as 0.78 per 100,000 exposures.¹¹ In dentistry, the 0.2% concentration is the most studied and effective antiplaque and antigingivitis agent due to its low toxicity and broad-spectrum antibacterial activity, while the 0.12% concentration is commonly used in mouthwashes.¹² CHX is effective against bacteria, viruses, and fungi and it is bacteriostatic at low concentrations and rapidly bactericidal at higher concentrations.¹³

CHX's bacteriostatic properties stem from its positively charged bisguanide structure, which strongly binds to negatively charged bacterial cell membranes and pellicle proteins. This binding increases membrane permeability, precipitates intracellular components, and ultimately leads to bacterial cell death.¹ A clinical study demonstrated that CHX gargle application significantly reduced aerosolized bacteria released into the environment during ultrasonic cleaning.¹⁴ In addition this binding is also considered a potential mechanism underlying tissue and tooth discoloration.³

CHX has been used for over 50 years; however, studies have demonstrated that its toxic properties affect not only bacteria but also host cells in a time- and dose-dependent

manner, which is a well-known and undesirable effect. In vitro studies have shown that CHX exerts a concentration- and time-dependent cytotoxic effect on the proliferation of host cells.^{15,16} Additionally, CHX has been shown to impair the normal function of fibroblasts by inhibiting their interaction with collagen fibers.¹⁷ A study evaluating the cytotoxicity of CHX on a human osteoblast cell line reported a decrease in the average percentage of viable cells with increasing application time.¹⁶ Giannelli et al.¹⁵ found that CHX is highly cytotoxic to osteoblastic, endothelial, and fibroblastic cells and cautioned against its use.

In addition to its cytotoxic effects, CHX, despite its widespread use, has been associated with a variety of relatively rare but clinically significant adverse events. Various adverse effects, including contact dermatitis, urticaria, photosensitivity reactions, asthma attacks, and anaphylactic shock, have been reported following the use of CHX preparations.¹⁰ The increasing number of reports of systemic and dental reactions in recent years suggests that adverse events may be more common than previously believed among individuals using CHX. While delayed-type hypersensitivity reactions are the most common, in rare cases, more severe clinical conditions requiring emergency intervention can also occur. Case reports have documented adverse reactions associated with the topical oral use of CHG.^{12,18} One case report described anaphylactic shock in a patient who developed a periodontal abscess after rinsing the mouth with hydrogen peroxide solution followed by a gargle

containing CHX.¹⁹ Another study documented a severe anaphylactic reaction to CHX in a dentist with over 20 years of practice and reported a total of 14 cases of occupational CHX-related allergies among healthcare workers.¹⁸ Another study reported that fixed drug eruption occurred after using mouthwash containing CHX.²⁰ The prevalence of adverse reactions associated with CHX is not precisely known. Therefore, this study aims to characterize the profile of adverse events related to CHX and CHX-containing products used for dental or oral indications, as reported in the FAERS database. In our study, 18 cases resulted in death following CHX use; moreover, a significant number of cases required hospitalization and were classified as serious adverse events, including those necessitating emergency intervention, life-threatening conditions, permanent disability, or congenital anomalies.

Adverse dental and oral events associated with CHX use include discoloration of teeth, mucosa, and restoration surfaces, particularly after prolonged and repeated use; dry mouth; altered taste sensation; pain; irritation; and desquamation of the oral mucosa.^{5,21} The discoloration of teeth is thought to be caused by the formation of metallic sulfides due to pellicle protein denaturation.³ A clinical study reported that the use of CHX gargle was highly effective in preventing plaque accumulation and gingival inflammation; however, it was associated with external staining and the development of supragingival calculus.²² Furthermore, more than half of the participants experienced adverse events during the experimental period. In another clinical study, diabetic patients underwent lavage with 0.12% CHX following non-surgical periodontal treatment, followed by home mouthrinse for four months. In this study, 31% of participants reported side effects, with the most frequently reported being taste changes, tooth staining, mouth and/or throat pain, tongue irritation, and wheezing or shortness of breath.²³ One case report described a pronounced delayed-type hypersensitivity reaction characterized by well-defined erythematous lesions on the gingiva following the use of CHG-containing toothpaste and mouthrinse. The study emphasized that clinicians should be aware that even low concentrations of CHX-containing oral hygiene products can induce hypersensitivity reactions.²⁴ A letter to the editor reported that although CHX solutions are commonly used for oral care in intensive care units, a clinical study found a high incidence (9.8%) of oral mucosal lesions in patients treated with 2% CHX digluconate. These lesions—including erosions, ulcerations, plaque formation, and mucosal bleeding—resolved completely after discontinuation of the agent, while no such adverse effects were observed with 0.12% or 0.20% CHX.²⁵ It was reported that the occurrence of adverse effects in patients treated with 2% CHX was associated with male gender and longer exposure to 2% CHX, suggesting a possible dose-response relationship. Additionally, increased CHX exposure has been linked to a higher risk of developing oral mucosal lesions in contact areas. In our study, the

most common side effects were tooth discoloration and dry mouth, consistent with the literature. It is also thought that the administration site conditions side effects observed in our study may be related to the local use of the chip form included in the product. Furthermore, although our study found no significant gender-related differences, it is noteworthy that the vast majority of cases involved women. Additionally, although serious adverse effects were reported in the 12–17 age group, only four participants in the study belonged to this age range. The possible reasons for this may include the more limited use of chlorhexidine in pediatric and adolescent populations compared to adults, as well as the fact that only serious events are typically reported to the database. Similarly, a study evaluating immediate allergic reactions to chlorhexidine in pediatric patient groups using the French pharmacovigilance database also reported a low number of cases, likely due to underreporting and insufficient awareness of the allergy. However, in this study, reactions were most frequently reported after at-home application of chlorhexidine for wound care.²⁵

This study identified multiple disproportionate signals for adverse events associated with CHX use based on FAERS data, suggesting that certain reactions were reported more frequently compared to other drugs. A significantly high ROR was observed for taste disturbance and tooth discoloration, indicating a strong reporting association between CHX and these adverse events. Consistent with our results, in a clinical trial, diabetic patients underwent lavage with 0.12% CHX after non-surgical periodontal treatment, followed by in-home mouthwash use for four months. In this study, 31% of participants reported adverse events; the most frequently reported were taste changes, tooth staining, mouth and/or throat pain, tongue irritation, and wheezing or dyspnea.²⁶ The high ROR values for these adverse events, including dysgeusia, are biologically plausible given the well-documented local effects of CHX on oral tissues. These adverse events are likely related to CHX binding to tissues, its prolonged efficacy, and its effect on taste receptors. A high reporting signal for anaphylactic reactions, although less frequent, is clinically significant due to its potential seriousness. Previous case reports have described hypersensitivity reactions to CHX, supporting the biological rationale of this finding.^{18,19} The pregnancy-related outcomes, defined as maternal exposure during pregnancy and premature delivery, demonstrated an elevated ROR, indicating disproportionate reporting among CHX-exposed cases in the FAERS database. This finding should be interpreted with caution, as FAERS does not provide information on exposure timing, dosage, route of administration, or underlying maternal and fetal risk factors. Moreover, reports categorized as maternal exposure during pregnancy may reflect precautionary or administrative reporting rather than confirmed adverse drug effects. In addition, although CHX is characterized by minimal systemic absorption, the observed disproportionality signal for pregnancy-related outcomes may be influenced by heightened reporting sensitivity during pregnancy. Healthcare professionals may be more

likely to report any exposure occurring during pregnancy, particularly in the absence of clear safety data. Therefore, the observed reporting signal should not be interpreted as evidence of an increased risk of preterm birth but rather as a pharmacovigilance signal warranting further investigation.

Due to the retrospective nature of this study, causal relationships cannot be established. RORs reflect reporting disproportionality rather than true incidence or risk, and therefore causality cannot be inferred. Additionally, the objectivity and completeness of the reported data may be limited, as the FAERS database is subject to underreporting, reporting bias, and incomplete or inaccurate case documentation. Furthermore, the spontaneous reporting system is inherently vulnerable to confounding factors, including variations in reporting practices, differential awareness among reporters, and the absence of standardized clinical verification. In addition, this study only considered the presence or absence of other pharmacological agents and did not perform a detailed evaluation of potential drug interactions. Information regarding individuals' systemic conditions at the time of or shortly before chlorhexidine use was unavailable. These factors may influence the occurrence and interpretation of adverse events and should be considered when contextualizing the findings. Despite these constraints, the present study has several notable strengths. Identifying disproportion signals for CHX, a commonly used dental prosthetic, could help increase clinical awareness, support pharmacovigilance studies, and promote cautious use in sensitive patient populations. Our research provides a valuable reference for managing adverse reactions caused by CHX. Restricting the analysis to cases in which CHX was used specifically for dental or oral indications allowed for a more targeted evaluation of adverse events relevant to dental practice. Moreover, the systematic classification of reported adverse events into dental/oral and systemic categories enabled a clearer characterization of CHX's safety profile within the context of oral health care. Importantly, by utilizing a large pharmacovigilance database, this study offers comprehensive real-world evidence and contributes to raising awareness of both common and less recognized adverse effects associated with CHX, a widely used antiseptic agent in dentistry. These findings may support clinicians in conducting risk-benefit assessments and promote more informed and cautious use of CHX in dental practice.

In conclusion, although CHX is an effective adjunctive agent in periodontal treatment, its duration of use, dosage, and indications should be carefully evaluated. Given the widespread use of CHX products, it is crucial that prescribing clinicians recognize and appropriately manage the clinical presentations of CHX-related hypersensitivity reactions.

Conclusions

CHX is a widely used antiseptic agent and is considered the universally accepted gold standard due to the scarcity of reported adverse events and the extensive literature

supporting its therapeutic efficacy. Although hypersensitivity and other adverse reactions to CHX are rare, the potential for anaphylactic shock should not be overlooked. Clinicians should remain vigilant for rare but severe allergic reactions, take thorough patient histories to identify potential triggers, carefully review prescribing indications, inform patients about possible side effects, and develop management plans for adverse events. Future research should focus on optimizing antiseptic protocols, developing new agents and administration methods, and investigating the long-term outcomes and efficacy of these agents across diverse populations and surgical disciplines, including special populations such as pregnant individuals.

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Conflicts of Interest Statement

No competing interests.

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