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Real-World Sodium Fluoride Safety Signals: Dual-Database Pharmacovigilance

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ABSTRACT

Introduction and aims: Sodium fluoride is widely used in preventive dentistry, yet its global safety profile has not been comprehensively characterised using real-world data. This study aimed to characterise reporting patterns and safety signals associated with sodium fluoride through an integrated pharmacovigilance analysis of the FDA adverse event reporting system (FAERS) and the World Health Organization (WHO) VigiBase.

Methods: Adverse event (AE) reports related to sodium fluoride were extracted from FAERS (2004-2024) and VigiBase (1971-2024). Reporting characteristics, including demographic distributions, reporter type, and event seriousness, were summarised descriptively. AEs were coded using the medical dictionary for regulatory activities (MedDRA) at the preferred term (PT) and system organ class (SOC) levels. Disproportionality-based signal detection was performed using multiple algorithms, and cross-database validation was applied to evaluate signal consistency and database-specific reporting features.

Results: Reporting patterns differed between the two systems: FAERS reports were predominantly submitted from the United States and by consumers, whereas VigiBase reports were mainly from Europe, with a higher proportion of health care professionals reporting. Reports involving female individuals were more frequently observed in both databases. Safety signals were primarily concentrated in oral and dental conditions, including dental fluorosis and acute oral mucosal reactions. Overall, 122 shared safety signals were identified across the two databases, with 62% involving oral or dental tissues. Adult populations accounted for a substantial proportion of reported signals, and a high proportion of reports were classified as serious, with predominantly early reported onset intervals.

Conclusion: This dual-database pharmacovigilance analysis identified consistent sodium fluoride-associated safety signals with a predominant oral and dental focus, alongside notable geographic and demographic reporting differences. Cross-database validation highlighted complementary strengths of FAERS and VigiBase for global safety surveillance of fluoride-containing dental products.

Clinical relevance: These findings support enhanced awareness of sodium fluoride-related safety patterns and may inform targeted monitoring strategies in preventive dental practice.

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Introduction

Sodium fluoride is a cornerstone preventive agent in modern dentistry, with applications ranging from daily oral hygiene products to professional therapeutic interventions. The World Health Organization (WHO) includes fluoride in its list of essential medicines, and major international dental organisations endorse sodium fluoride for caries prevention and dentinal hypersensitivity management.[1] Nevertheless, substantial global disparities exist in regulatory frameworks, clinical protocols, and safety surveillance and monitoring systems. While developed nations maintain comprehensive pharmacovigilance infrastructures, resource-limited regions often lack the capacity for systematic fluoride safety surveillance.[2] Controlled clinical studies have confirmed sodium fluoride's preventive efficacy and acceptable safety margins; however, their limited sample sizes, short follow-up periods, and standardised designs may not adequately reflect real-world safety reporting characteristics across heterogeneous populations and diverse clinical contexts.[3]

In this context, real-world pharmacovigilance provides indispensable complementary evidence to clinical trials by detecting rare and long-term adverse events (AEs) through large-scale safety reporting systems.[4] The U.S. Food and Drug Administration adverse event reporting system (FAERS) and the WHO Global Pharmacovigilance Database (VigiBase) represent the two most comprehensive international AE surveillance platforms.[5] FAERS predominantly captures North American consumer and patient-submitted reports, which facilitates the identification of acutely reported adverse reactions.[6] Conversely, VigiBase integrates multinational reports, primarily from health care professionals, enabling the recognition of broader and potentially longer-term safety patterns.[7] These structural and geographic differences form a valuable foundation for cross-platform validation and global comparison of sodium fluoride-related safety reporting patterns.[8]

Despite the widespread clinical use of sodium fluoride, existing safety studies have largely focused on acute toxicity case reports and dental fluorosis epidemiology, while comprehensive safety profiles, population-level reporting characteristics, and international reporting trends remain underexplored.[9] Furthermore, current pharmacovigilance frameworks for fluoride-containing agents are underdeveloped, and clinicians lack standardised, data-informed tools for systematic safety surveillance. Consequently, fluoride prescriptions often rely on empirical judgment rather than integrated real-world safety evidence, potentially increasing the likelihood of AEs being underrecognised or inconsistently reported.[10] Global inconsistencies in sodium fluoride usage policies and monitoring criteria further hinder unified safety assessment from a pharmacovigilance perspective.[11-14]

Therefore, this study aimed to characterise the international safety reporting patterns and pharmacovigilance signals of sodium fluoride by integrating real-world data from FAERS and VigiBase. Through cross-database validation, we sought to systematically describe the occurrence patterns, demographic distributions, and system-specific susceptibilities of sodium fluoride-related AEs. This approach enhances signal reliability, mitigates database-specific bias, and provides a comprehensive global perspective on sodium fluoride safety surveillance. The resulting evidence is expected to support safety awareness, targeted monitoring strategies, and the development of harmonised international frameworks for preventive dental practice.

Materials and methods

Data sources and case identification

This retrospective pharmacovigilance study integrated individual case safety reports (ICSRs) from two international spontaneous reporting systems: the FAERS (https://fis.fda.gov/) and the VigiBase (https://www.vigiaccess.org/).[15,16] The FAERS contains 21,964,449 raw AE submissions from January 2004 to September 2024, whereas the WHO global safety database VigiBase contains 117,935,336 ICSRs from 1971 to December 2024. In spontaneous reporting systems, the report, rather than the patient, serves as the analytical unit. Thus, a single patient may generate multiple ICSRs, and each ICSR may document several distinct AE terms. FAERS submissions were deduplicated according to FDA guidelines by retaining the most recent version of each case and removing entries listed in the quarterly deleted-case files, yielding 18,278,243 unique ICSRs.[15] VigiBase data were accessed through VigiAccess, which provides fully standardised and deduplicated ICSRs curated by the Uppsala Monitoring Centre (UMC),[16] thus retrieved and unique report counts are identical.

Sodium fluoride-related cases were identified by standardising drug names using the WHO Drug Dictionary (B3, September 2024) and selecting ICSRs in which sodium fluoride was coded as the primary suspect (PS) drug.[17] This process yielded 3053 PS-defined ICSRs in FAERS and 1883 in VigiBase. These PS reports formed the basis for all subsequent AE extraction, descriptive analyses, disproportionality assessments, and cross-database concordance evaluations. A schematic workflow is presented in Figure 1.

AE extraction and statistical processing

AE coding and variable definition

AE terms were standardised to preferred terms (PTs) and system organ classes (SOCs) using the medical dictionary for regulatory activities (MedDRA; version 27.0).[18] Because each ICSR may contain multiple MedDRA-coded AEs, the number of PT-level AE terms exceeds the number of PS reports. In total, 10,095 PT-level AEs were extracted from the 3053 FAERS PS-defined ICSRs, and 4422 PT-level AEs were extracted from the 1883 VigiBase PS-defined ICSRs (Figure 1).

Descriptive statistical analysis

Analytical variables included demographic characteristics, geographic region, reporter type, seriousness criteria, and SOC/PT distributions. Age categories were harmonised across databases using the FAERS age-band structure (<18, 18-44, 45-64, ≥65 years) to ensure comparability in stratified analyses. Descriptive statistical analyses were used to summarise reporting characteristics, demographic patterns, and AE

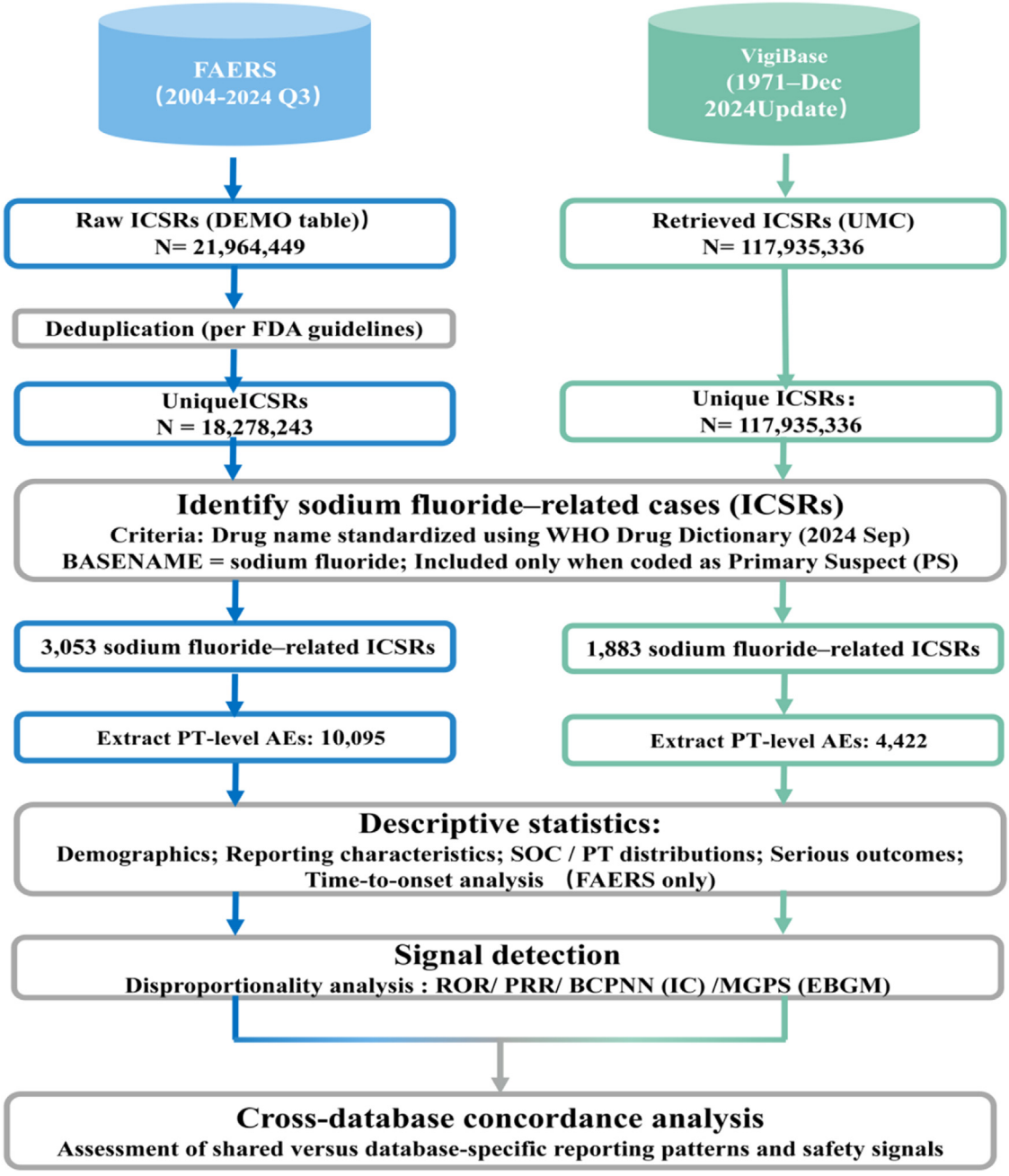

Fig. 1 – Study workflow for data processing and identification of sodium fluoride-associated adverse event (AE) reports in FAERS and VigiBase. Individual Case Safety Reports (ICSRs) were extracted from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the WHO global pharmacovigilance database VigiBase. FAERS raw submissions were deduplicated according to FDA guidelines to obtain unique reports, whereas VigiBase provides standardised and pre-deduplicated ICSRs curated by the Uppsala Monitoring Centre (UMC). Sodium fluoride-associated ICSRs were identified using the WHO drug dictionary based on primary suspect (PS) drug coding. Adverse events (AEs) were mapped to MedDRA preferred terms (PTs) for descriptive analyses, and disproportionality analyses (reporting odds ratio [ROR], proportional reporting ratio [PRR], Bayesian confidence propagation neural network/information component [BCPNN/IC], and empirical Bayes geometric mean [EBGM]) were conducted for signal detection. Time-to-onset (TTO) analysis was performed in FAERS only, owing to the availability of structured treatment start and event onset dates. All counts shown in the workflow represent reports or AE terms rather than individual patients.

distributions.[19] All analyses were conducted using SAS version 9.4 (SAS Institute Inc), and data visualisation was performed using the ggplot2 package in R software.[20]

Time-to-onset analysis

Time-to-onset (TTO) analysis using Weibull shape parameter modelling was conducted exclusively in FAERS because

VigiBase does not provide structured treatment start dates or AE onset timestamps. TTO was defined as the interval between the reporter-documented therapy start date (START_DT) and AE onset date (EVENT_DT), characterising the temporal pattern of the reported exposure episode rather than the biological latency associated with chronic fluoride exposure. Reports containing missing, invalid, or negative date values were excluded in accordance with established pharmacovigilance procedures.[21]

Signal detection methodology

Disproportionality-based signal detection framework

Disproportionality analyses were performed independently for FAERS and VigiBase using four established algorithms: the reporting odds ratio (ROR),[22] proportional reporting ratio (PRR),[23] Bayesian confidence propagation neural network (BCPNN) generating the information component (IC),[24] and the empirical Bayes geometric mean (EBGM) derived from the multi-item gamma Poisson shrinker model (MGPS).[25] Detailed formulas for each method are provided in Supplementary Table S1. For each drug–AE pair, a 2 × 2 contingency table was constructed, where a represented the number of reports containing both sodium fluoride and the specific adverse reaction, b denoted reports containing sodium fluoride with other AEs, c indicated reports involving other drugs with the specific AE, and d corresponded to reports including other drugs and other AEs.[22-25]

Signal positivity criteria

A safety signal was considered present only when all predefined criteria were simultaneously met: at least three coreported cases ($a \geq 3$), a lower 95% confidence interval (CI) bound for the ROR > 1, PRR ≥ 2 with chi-square (χ^2) ≥ 4, IC_{025} > 0, and $EBGM_{05}$ > 2.[22-25] These conservative, multiparameter thresholds are widely applied in pharmacovigilance to minimise false-positive findings in spontaneous reporting datasets. The use of different threshold metrics reflects the statistical foundations of each algorithm: ROR is interpreted using CI, PRR follows the MHRA-recommended framework combining PRR magnitude with χ^2 testing, and signal detection based on incorporates Bayesian shrinkage through the lower credibility bound (IC_{025} > 0 and $EBGM_{05}$>2).

Stratified disproportionality analyses

To evaluate subgroup-specific variation in disproportional reporting, stratified ROR analyses were additionally performed using FAERS data, which include age group, sex, and reporter type. ROR values with corresponding 95% CIs were recalculated within each stratum using the same computational framework applied in the primary signal detection analysis. These analyses were conducted to assess heterogeneity in reporting tendencies and to contextualise subsequent disproportionality estimates.

Interpretation and stability considerations

High ROR values derived from small numbers of reports were evaluated through multialgorithm concordance, cross-database replication, and reference to established fluoride toxicology.[19,22] To avoid misinterpretation of disproportionality measures as evidence of causality, all signal detection results in this study are interpreted strictly as statistical associations reflecting disproportionate reporting patterns. These signals are hypothesis-generating in nature and require confirmation through dedicated pharmacoepidemiologic investigations.

Cross-database validation analysis

Cross-database validation analysis was performed to assess signal consistency between FAERS and VigiBase datasets and to identify overlapping and unique safety profiles.[26] The top 50 PTs ranked by ROR and report frequency were compared to assess signal concordance across the two platforms. Venn diagram-based visualisation was used to illustrate concordance patterns and to strengthen the interpretation of validated safety signals across two independent pharmacovigilance systems.

Results

Global reporting characteristics of sodium fluoride-associated AEs

Temporal trends in reporting

Over the past two decades, FAERS database reporting activity began modestly, with 28 reports recorded in 2004 (Figure 2A). Reporting increased substantially, reaching a peak of 480 reports in 2008, followed by a gradual decline through 2022 (46 reports) (Figure 2A). An increase in reporting volume was observed in 2023 and 2024, with 109 and 226 reports, respectively (Figure 2A). VigiBase data, spanning a longer historical window, demonstrated a different temporal pattern. Annual reports before 2005 generally remained below 30, with increased reporting activity observed after 2008 (Figure 2B). From 2015 onward, reporting levels remained elevated, reaching 152 reports in 2023 (Figure 2B).

Geographic distribution of reported AEs

Both systems revealed that sodium fluoride-associated AEs originated predominantly from the Americas and Europe. FAERS reports came mainly from the Americas (88.40%), with smaller contributions from Europe (5.76%), Asia (1.87%), Oceania (1.05%), and Africa (0.13%), while 2.78% remained unspecified (Figure 2C) (Supplementary Tables S2). In contrast, VigiBase displayed a more balanced geographic distribution. Reports were primarily submitted from Europe (65.69%) and the Americas (31.44%), with smaller contributions from Asia (1.43%), Africa (0.37%), and Oceania (0.06%) (Figure 2C) (Supplementary Tables S3).

Age distribution of reports

Adult age groups accounted for the majority of sodium fluoride-associated AE reports in both databases, although interpretation was limited by substantial proportions of missing age information (FAERS: 42.88%; VigiBase: 32.24%). To facilitate cross-database comparison, age distributions were analysed using harmonised life-stage categories (<18, 18-44, 45-64, and ≥65 years).

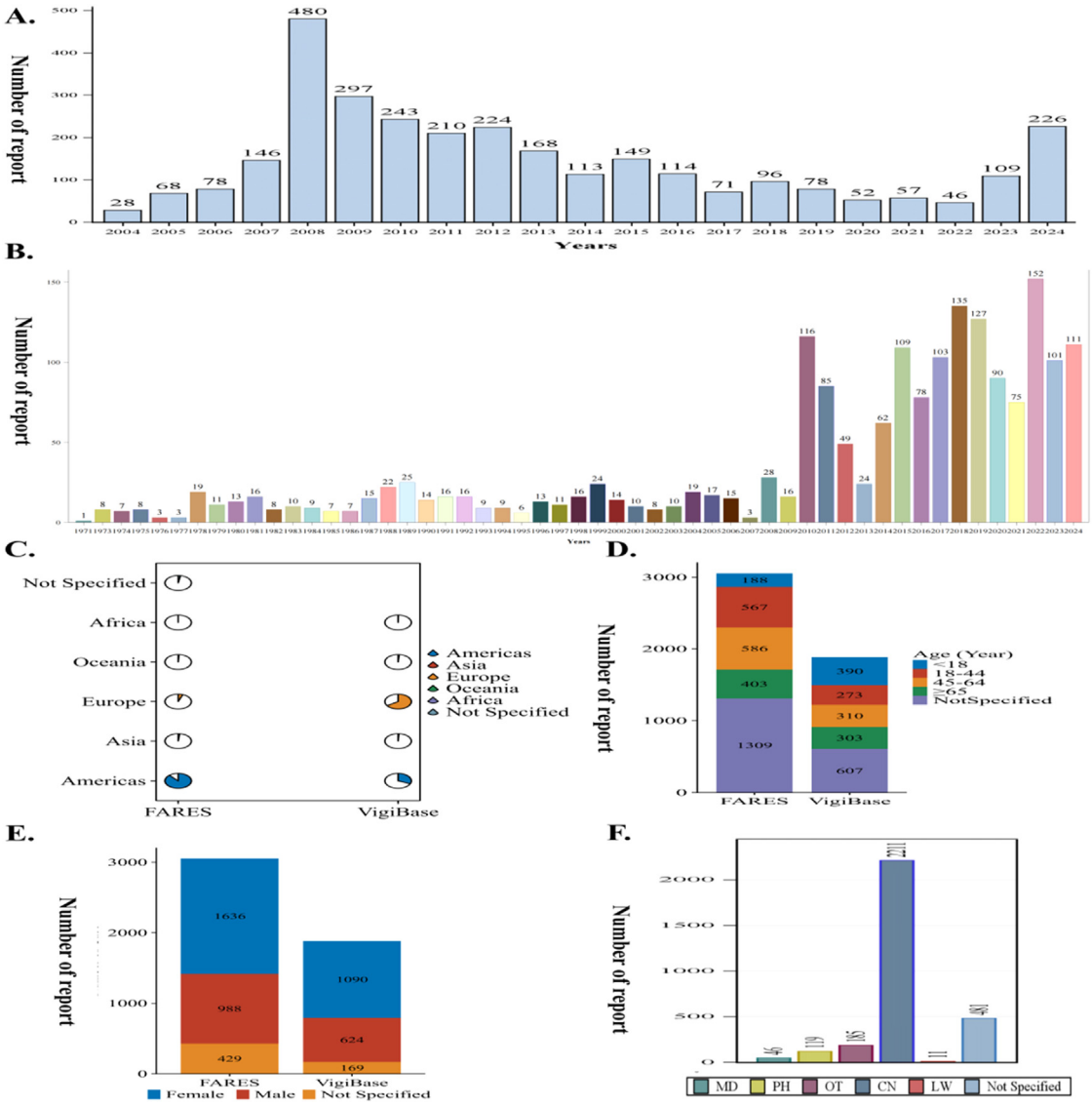

Fig. 2 – Temporal trends and demographic characteristics of sodium fluoride-associated AE reports in FAERS and VigiBase. A and B, Annual reporting trends of sodium fluoride-related reports in FAERS (2004-2024) and VigiBase (1971-2024). C, Geographic distribution of reports across continents. D, Sex distribution of reports in both databases. E, Age distribution of reports after harmonisation into four broad life-stage categories (<18, 18-44, 45-64, and ≥65 years) to enable cross-database comparison; VigiBase age data, originally recorded using WHO-standard age bands, were aggregated accordingly. F, Reporter types in FAERS. All counts represent individual case safety reports rather than individual patients. CN, consumer; LW, lawyer; MD, pharmacist; OT, other health-professional; PH, physician.

In FAERS, among reports with documented age, individuals aged 45 to 64 years constituted the largest proportion (19.19%, *n* = 586), followed by those aged 18 to 44 years (18.57%, *n* = 567). Reports involving individuals aged ≥65 years accounted for 13.20% (*n* = 403), whereas paediatric reports (<18 years) comprised 6.16% (*n* = 188) (Figure 2D; Supplementary Table S2).

After age harmonisation, VigiBase demonstrated a comparable adult-dominant distribution. Reports involving individuals aged 45 to 64 years accounted for 16.46% (*n* = 310), and those aged 18 to 44 years for 14.50% (*n* = 273). Paediatric reports (<18 years) constituted 20.72% (*n* = 390), while reports involving individuals aged ≥65 years accounted for 16.09% (*n* = 303) (Figure 2D; Supplementary Table S3). Within paediatric reports, cases were primarily concentrated among children aged 2 to 11 years, whereas reports involving older adults were distributed across the 65 to 74-year and ≥75-year categories (Supplementary Table S3).

Sex and reporter type distribution of reports

Reports involving female individuals accounted for a higher proportion of sodium fluoride–associated AE reports in both databases. In FAERS, 53.59% (*n* = 1636) of reports involved females, 32.36% (*n* = 988) involved males, and 14.05% (*n* = 429) lacked sex specification (Figure 2E). A similar pattern was observed in VigiBase, where 57.89% (*n* = 1090) of reports involved females, 33.14% (*n* = 624) involved males, and 8.98% (*n* = 169) were unspecified (Figure 2E).

Reporter type analysis in FAERS revealed that consumers submitted the majority of reports (72.42%, *n* = 2211), followed by other health professionals (6.06%, *n* = 185), physicians (3.90%, *n* = 119), and pharmacists (1.51%, *n* = 46) (Figure 2F, Supplementary Table S2). Legal representatives submitted 0.36% (*n* = 11) of reports, while 15.75% (*n* = 481) originated from unspecified sources.

FARES signal detection and reporting profiles

Because a single ICSR may contain multiple MedDRA-coded AE terms, SOC- and PT-level counts represent AE terms rather than unique reports and may exceed the total number of sodium fluoride PS reports. All findings in this section reflect statistical disproportional reporting patterns rather than clinical incidence, risk, or causality. Extremely high ROR values (>1000) derived from very small cell counts (eg, a or c <5) are subject to statistical instability, wide confidence intervals, and limited evidential strength and therefore require cautious interpretation.

SOC distribution and frequently reported PTs

Among the 27 SOC categories, gastrointestinal disorders represented the SOC with the highest number of PT-level AE terms in FAERS (*n* = 3611), accounting for 35.77% of all extracted PTs (Figure 3A). General disorders and administration site conditions ranked second (*n* = 1107), followed by injury, poisoning, and procedural complications (*n* = 1007) (Figure 3A).

The top 30 PTs ranked by reporting frequency are presented in Figure 3B. At the PT level, oral and dental manifestations predominated among sodium fluoride-associated AE terms (Figure 3B). Tooth discolouration was among the most commonly coded PTs (2.94%, *n* = 297). Other frequently coded PTs included oral discomfort (2.14%, *n* = 216), oral mucosal exfoliation (1.52%, *n* = 153), lip swelling (1.47%, *n* = 148), and stomatitis (1.46%, *n* = 147). Drug abuse, classified under psychiatric disorders, also appeared among the more frequently reported PTs (2.36%, *n* = 238). These SOC- and PT-level frequencies reflect the distribution of coded AE terms and do not indicate clinical incidence or causal associations.

Disproportionality-based signal detection of sodium fluoride-associated AEs

Among PT-level signals simultaneously positive across all four disproportionality algorithms (ROR, PRR, IC, and EBGM), the top 30 PTs were ranked according to ROR magnitude (Figure 3C; Supplementary Table S4). The strongest disproportionality was observed for chemical burn of the gastrointestinal tract (*n* = 33, ROR = 1729.84; 95% CI: 1168.22-2561.45), followed by oral mucosal exfoliation (*n* = 153, ROR = 699.02; 95% CI: 590.08-882.08) and tooth discolouration (*n* = 297, ROR =680.45; 95% CI: 602.23-768.84) (Figure 3C). In addition to these top-ranked signals, several PTs combined relatively high reporting frequency with elevated disproportionality, including application-site burn (*n* = 154, ROR = 188.43), gingival pain (*n* = 125, ROR = 98.35), and oral discomfort (*n* = 216, ROR = 96.66). These PTs formed a prominent cluster within the FAERS sodium fluoride PS reporting profile (Figure 3B and C).

Conversely, several PTs exhibited very high ROR estimates despite being derived from small numbers of PT-level terms, such as chemical burn of the oral cavity (*n* = 6, ROR = 529.25), fluorosis (*n* = 4, ROR = 341.82), application-site anaesthesia (*n* = 4, ROR = 321.41), mucosal exfoliation (*n* = 4, ROR = 307.64), and enamel anomaly (*n* = 6, ROR = 119.22). These PTs are presented to illustrate the full spectrum of statistically detected signals but should be interpreted with caution owing to sparse data and statistical instability (Figure 3C; Supplementary Table S4).

Overall, the FAERS signal landscape for sodium fluoride PS reports was characterised by disproportionately reported PTs

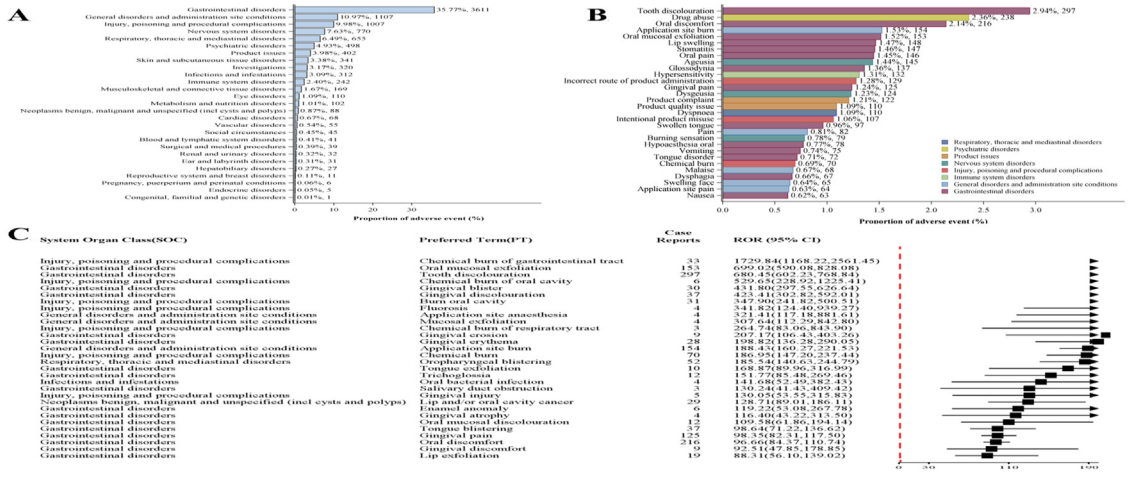

Fig. 3 – System organ class (SOC)- and preferred term (PT)–level signal profiles of sodium fluoride-associated adverse events (AEs) in the FAERS database. A, Distribution of AEs across 27 SOC categories, ranked by the proportion of reports. B, Top 30 PTs ranked by report frequency, illustrating the most frequently reported sodium fluoride-associated AEs. C, Forest plot of the top 30 PT-level signals simultaneously positive across all four disproportionality algorithms, ranked by reporting odds ratio (ROR). Error bars represent 95% confidence intervals for ROR. Only PTs meeting predefined signal positivity criteria across all methods are shown.

predominantly related to chemical injury and oral or gastrointestinal mucosal alterations, as reflected by relative disproportionality metrics and reporting frequencies, without implying incidence rates or causal relationships.

Age-stratified signal analysis

Age-stratified analysis (Figure 4) demonstrated that oral and mucosal-related AEs occurred across all age groups, though specific PT patterns varied by age category. Core PTs, including tooth discolouration, oral discomfort, application-site burn, and oral mucosal exfoliation, consistently showed elevated ROR values across age strata.

However, the relative frequency of certain events differed between age categories. In reports involving individuals aged <18 years, the most frequently coded PTs included vomiting, accidental exposure, and hypersensitivity. Among reports

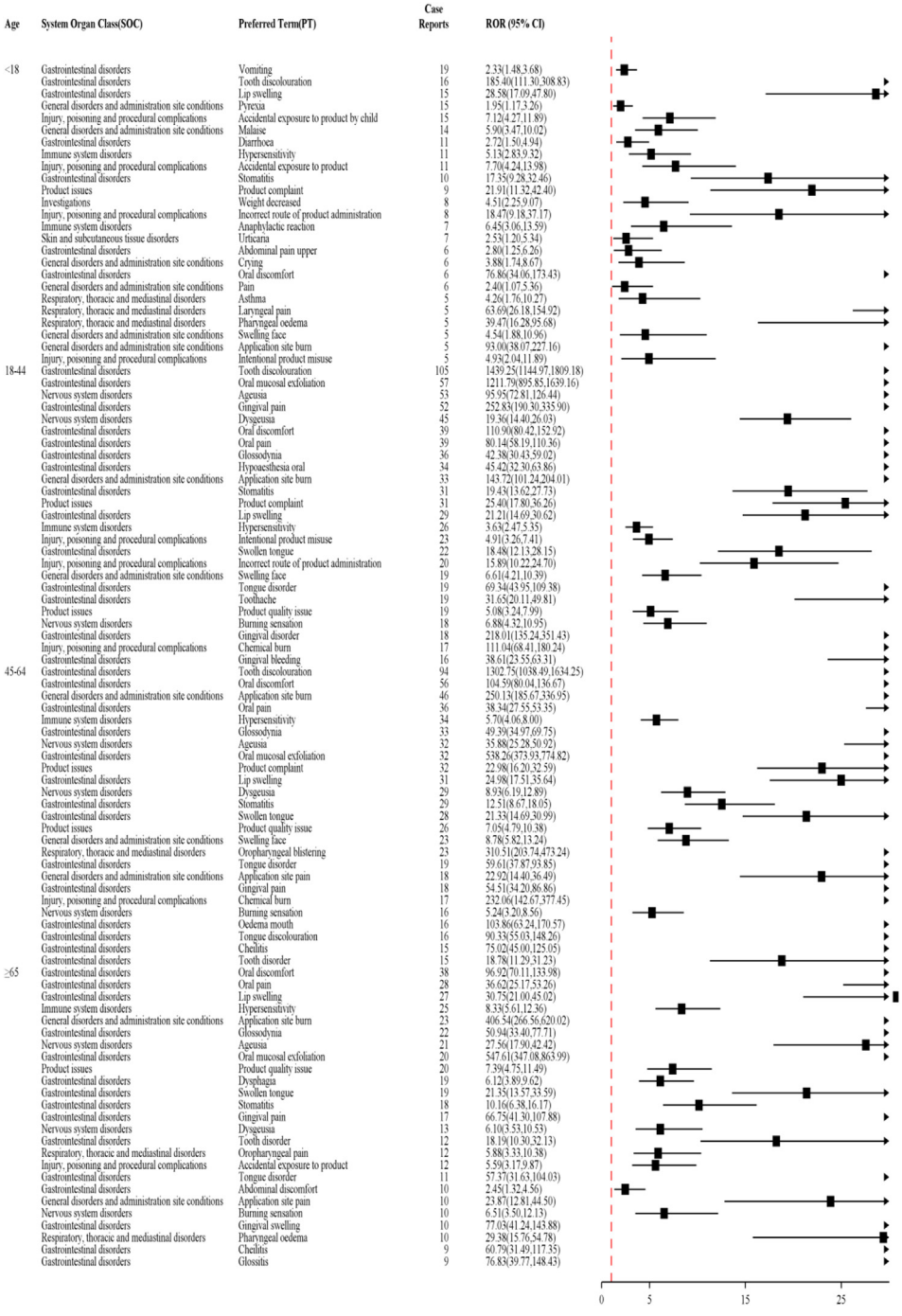

Fig. 4 – Age-stratified preferred term (PT)-level adverse event signals associated with sodium fluoride in the FAERS database. Forest plots present the top 25 PT-level terms within each age group (<18, 18-44, 45-64, and ≥65 years), ranked by report frequency. Only PTs simultaneously positive across four disproportionality algorithms are shown. Squares indicate ROR estimates with 95% confidence intervals.

involving individuals aged 18 to 44 years, oral discomfort, ageusia, and glossodynia were more frequently coded. Reports involving individuals aged 45 to 64 years showed a heterogeneous distribution of mucosal and sensory PTs, with cheilitis, stomatitis, and dysgeusia among commonly reported terms. In reports involving individuals aged ≥65 years, oral mucosal PTs remained prominent, with additional occurrences of dysphagia, odynophagia, and xerostomia. Together, age-stratified results reflected differences in reporting patterns rather than differences in underlying biological risk. Paediatric reports were more frequently characterised by acute exposure-related terms, whereas adult reports more commonly included sensory, discomfort-related, or functional impairment-related PTs.

Demographic and reporter-type stratification

Sex-stratified analyses revealed comparable signal patterns between reports involving female and male individuals, with tooth discolouration, oral discomfort, and application-site burn consistently among the most frequently reported PTs (Supplementary Figure S1). Reports involving female individuals showed a higher number of coded mucosal and sensory-related PTs, including stomatitis and glossodynia, whereas reports involving male individuals exhibited slightly higher ROR values across a broader range of inflammatory and administration-related PTs.

Reporter-type analysis demonstrated broadly consistent signal distributions across different reporting sources (Supplementary Figure S2). Reports submitted by health care professionals more frequently involved objectively verifiable PTs such as application-site burn, oral mucosal exfoliation, and lip swelling, while consumer-submitted reports more commonly described subjective symptoms, including taste disturbance, oral pain, and dry mouth. These demographic and reporter-type patterns represent reporting tendencies rather than biological risk differences or causal effects.

Temporal characteristics of reported time-to-onset

TTO analysis was conducted using FAERS reports containing valid therapy start and adverse event onset dates (Figure 5A-C; Supplementary Tables S2 and S5). Among 1232 reports with complete date fields, the median reported TTO was 1.0 day (IQR 0.0-22.0), with 32.8% of events reported within 30 days of the reporter-documented exposure episode. Reporting frequency declined thereafter, with 5.84% of events occurring between 31 and 60 days, 2.35% between 61 and 90 days, and 5.60% beyond 360 days (Figure 5A). The cumulative onset curve showed a steep initial increase followed by an early plateau within the first month (Figure 5B), indicating a concentration of reported onset times during the early reporting window. Sex-stratified analyses showed no observable differences in TTO distributions between reports involving male and female individuals ($P = 0.4322$), with both groups exhibiting an identical median reported TTO of 1.0 day (IQR 0.0-22.0) (Figure 5C). These TTO metrics characterise reporting dynamics associated with time-defined exposure episodes documented in FAERS rather than biological latency related to chronic or continuous fluoride exposure.

Distribution of serious outcomes

Among all FAERS sodium fluoride primary suspect reports, 82.87% (n = 2530 reports) met FDA criteria for serious outcomes, while 17.13% (n = 523 reports) were classified as non-serious (Figure 5D). Within serious-outcome reports, hospitalisation was the most frequently recorded category (7.44%, n = 227), followed by disability (3.77%, n = 115), death (2.19%, n = 67), and life-threatening events (1.34%, n = 41)

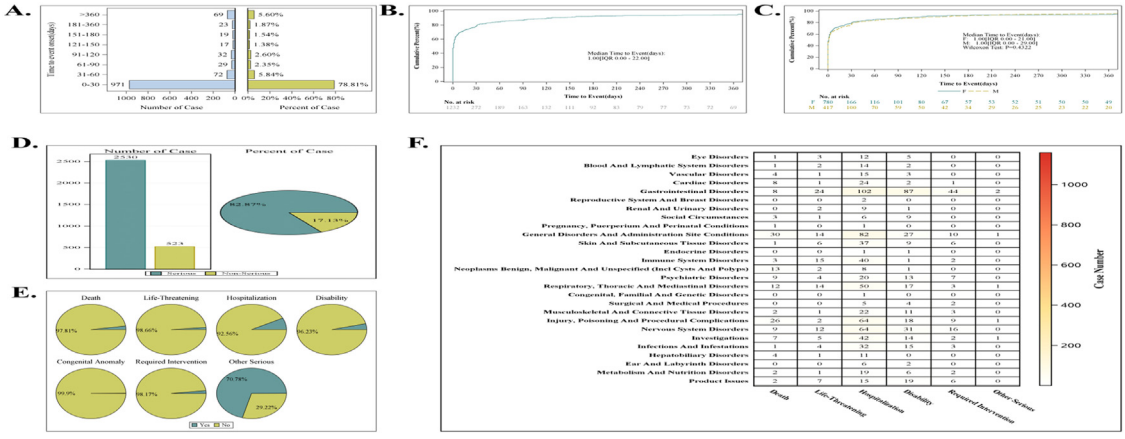

Fig. 5 – Reported temporal characteristics and seriousness distribution of sodium fluoride-associated adverse events (AEs) in the FAERS database. A, Time-to-onset (TTO) distribution based on reports with valid date fields, indicating that 78.81% of reported events occurred within 30 days. B and C, Cumulative onset curves illustrating the distribution of reported onset times and the absence of observable sex-related differences. D, Overall seriousness classification of reports according to FDA criteria. E, Distribution of serious outcomes, including hospitalisation, disability, and life-threatening events. F, System organ class (SOC) heatmap showing the organ-system distribution of serious-outcome reports. Note: TTO was defined as the interval between the reporter-documented therapy start date and adverse event onset date recorded in FAERS and describes temporal reporting patterns associated with time-defined exposure episodes rather than biological latency related to chronic or continuous fluoride exposure. VigiAccess does not contain these date fields and was therefore not included in TTO analyses.

(Figure 5E). Medical interventions were required in 1.83% (*n* = 56) of reports, and congenital anomalies were rare (0.10%, *n* = 3). The majority of serious reports (70.78%) were categorised as other serious outcomes (Figure 5E).

SOC-specific distribution of serious outcomes demonstrated that gastrointestinal disorders accounted for the largest number of serious outcomes (*n* = 356), including the highest frequencies of hospitalisation (*n* = 102), disability (*n* = 87), life-threatening events (*n* = 24), and required medical intervention (*n* = 44) (Figure 5F, Supplementary Tables S2). General disorders and administration site conditions, along with injury, poisoning, and procedural complications, had the highest numbers of reported deaths (*n* = 30 and *n* = 26, respectively), while other SOCs contributed proportionally fewer serious-outcome reports across all outcome categories.

Global signal characterisation of sodium fluoride-associated AEs in VigiBase

SOC and PT distribution in VigiBase

SOC-level analysis in VigiBase identified gastrointestinal disorders as the largest AE category, accounting for 38.42% (*n* = 1699) of reported PT-level terms, followed by general disorders and administration site conditions (10.04%, *n* = 44), and skin and subcutaneous tissue disorders (9.68%, *n* = 428) (Figure 6A, Supplementary Table S6). Compared with FAERS, VigiBase showed a relatively higher proportional representation of skin- and hypersensitivity-related PTs, reflecting differences in database coverage and reporting composition.

At the PT level, the most frequently reported events were oral discomfort (2.62%, *n* = 116), followed by hypersensitivity (2.26%, *n* = 100), rash (2.15%, *n* = 95), product taste abnormal (2.15%, *n* = 95), and vomiting (2.01%, *n* = 93) (Figure 6B). These PT-level frequencies represent reported AE terms rather than unique cases and describe reporting distributions within the global pharmacovigilance system.

Disproportionality-based signal profiles in the global database

Multialgorithm signal detection analysis identified multiple PTs meeting predefined signal positivity criteria across all four disproportionality methods (Figure 6C; Supplementary Tables S6). Fluorosis dental demonstrated the highest reporting disproportionality (ROR =14,383.1; 95% CI: 5735.74-36067.3), although this estimate was derived from very small cell counts (*n* = 7), resulting in wide CIs. Other highly ranked PTs included chemical burn of the gastrointestinal tract (*n* = 7, ROR = 2124.77; 95% CI: 983.53-4590.27), fluorosis (*n* = 4, ROR = 1503.85; 95% CI: 549.01-4119.31), and chemical burn of the oral cavity (*n* = 5, ROR = 1308.79; 95% CI: 533.05-3212.47). In contrast, several PTs combined moderate-to-high disproportionality with larger report counts, including oral mucosal exfoliation (ROR = 938.92, *n* = 56), product taste abnormal (ROR = 155.71, *n* = 95), tooth discolouration (ROR = 150.4, *n* = 53), and oral discomfort (ROR = 140.34, *n* = 116). These PTs constituted the most frequently reported oral manifestations within the VigiBase dataset and showed consistent signal detection across algorithms.

Several gingival-related PTs also demonstrated clustered signal patterns, including gingival injury (ROR = 352.39, *n* = 4), gingival blister (ROR = 312.48, *n* = 8), gingival discomfort (ROR = 277.11, *n* = 12), gingival ulceration (ROR = 220.49, *n* = 7), and gingival pain (ROR = 96.75, *n* = 41). Overall, PTs with extremely elevated ROR values were more frequently supported by sparse data, whereas PTs with lower ROR estimates tended to be reported more consistently across a larger number of reports. These results summarise statistically disproportionate reporting patterns observed in an international spontaneous reporting system and are presented to enable cross-database comparison with FAERS, without implying clinical incidence or causal relationships.

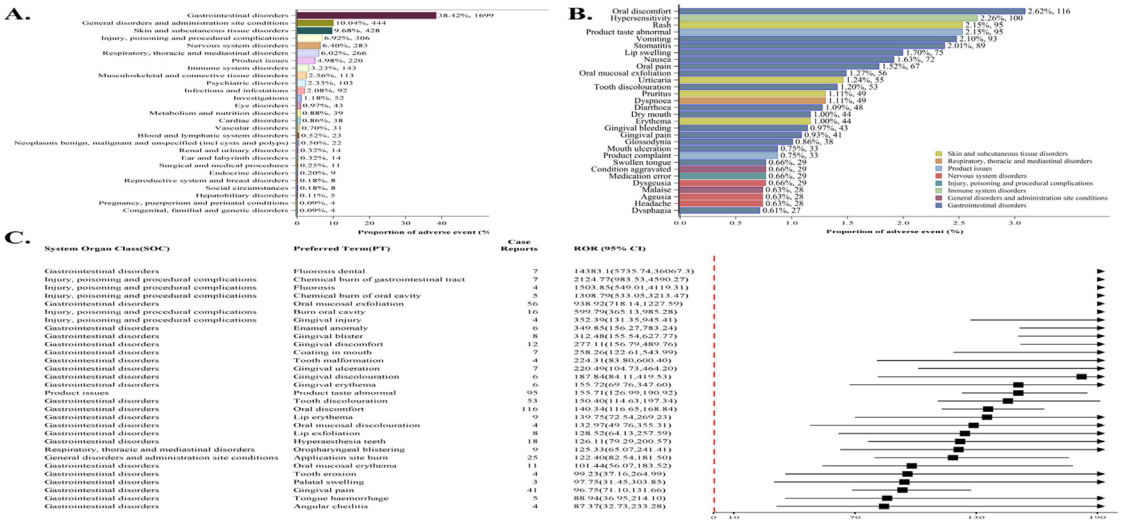

Fig. 6 – Signal detection analysis of sodium fluoride-related adverse events (AEs) in the VigiBase dataset. A, Distribution of adverse events across 27 system organ class (SOC) categories, ranked by the proportion of reports. B, Top 30 preferred terms (PTs) ranked by report frequency. C, Forest plot of the top 30 PT-level signals simultaneously positive across all four disproportionality algorithms, ranked by reporting odds ratio (ROR). Error bars represent 95% confidence intervals for ROR. Only PTs meeting predefined signal positivity criteria across all methods are shown.

Cross-database signal validation

Network-based intersection analysis of the Top 50 PTs revealed a set of overlapping oral and dental-related signals forming the central hub of shared signals between FAERS and VigiBase (Figure 7A). Comparison of signal strength across databases demonstrated concordant disproportionate reporting patterns for several key oral PTs. Tooth discolouration emerged as a highly ranked shared signal, exhibiting elevated disproportionality in both databases (FAERS: ROR = 680.45; VigiBase: ROR = 150.40), followed by oral mucosal exfoliation (FAERS: ROR = 699.02; VigiBase : ROR = 938.92) and chemical

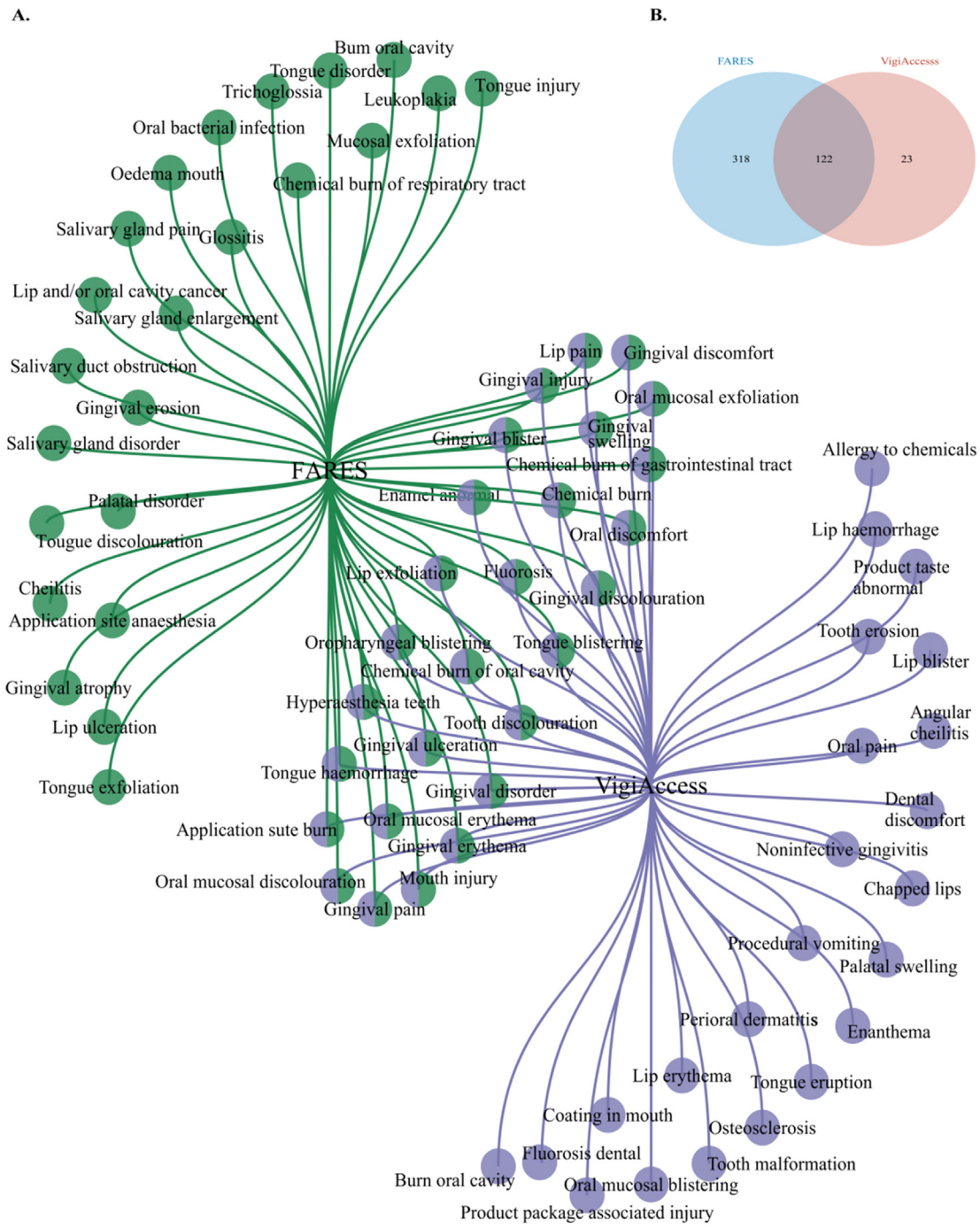

Fig. 7 – Cross-database signal intersection analysis of sodium fluoride–associated adverse events. A, Network visualisation of the top 50 preferred terms (PTs) identified in FAERS and VigiBase, showing PT-level signals unique to FAERS (green), unique to VigiBase (purple), and overlapping PTs detected in both databases. B, Venn diagram summarising the number of PT-level signals shared between FAERS and VigiBase and those unique to each database, with 122 shared signals, 318 signals unique to FAERS, and 23 signals unique to VigiBase. All signals were defined at the MedDRA PT level using identical criteria in both databases. Counts represent PT-level signals.

burn of the oral cavity (FAERS: ROR = 529.65; VigiBase: ROR = 1308.79) (Figure 7B). Dental fluorosis showed the highest disproportionality in VigiBase (ROR = 14383.16), and was also detected as a signal in FAERS, although with a lower relative ranking. Frequency-based intersection analysis further supported these patterns, with tooth discolouration, oral discomfort, and application-site burn consistently ranking among the most frequently reported PTs in both datasets (Supplementary Figure S3).

Intersection analysis identified 122 validated PT-level signals shared between FAERS and VigiBase databases, of which 76 (62%) represented oral or dental manifestations (Figure 7B). FAERS contributed 318 database-specific signals, whereas VigiBase contributed 23 unique signals, highlighting complementary coverage across national and global pharmacovigilance systems. Consistent with the age stratification findings, the intersecting signals predominantly involved adult populations across both databases. The shared sodium fluoride-related PTs primarily involved dental alterations (tooth discoloration, dental fluorosis, tooth erosion), gingival complications (gingival pain, swelling, bleeding), mucosal injuries (oral mucosal exfoliation, chemical burn of the oral cavity), and sensory disturbances (ageusia, glossodynia, coating in mouth), along with application-related events such as accidental exposure and application-site burns.

Discussion

This dual-database pharmacovigilance study characterises sodium fluoride-associated AE independent international surveillance systems. A total of 122 overlapping PT–level signals were identified, with 62% involving oral and dental manifestations, reflecting the predominance of oral- and dental-related reports within spontaneous reporting systems.[27,28] Beyond its local effects, the detection of AEs spanning multiple SOCs indicates the breadth of reports captured across global pharmacovigilance databases.[29] It should be emphasised that these findings reflect statistically disproportionate reporting patterns identified within spontaneous reporting systems and are intended to generate safety hypotheses rather than establish causal relationships or quantify clinical risk. Accordingly, the present findings describe real-world reporting patterns that may inform ongoing pharmacovigilance surveillance of fluoride-containing products.[30]

The epidemiological patterns identified in this analysis demonstrated marked geographic and demographic variation in sodium fluoride-associated AEs. The contrasting geographic distributions between FAERS (88.40% reports from the Americas) and VigiBase (65.69% from Europe) are consistent with inherent differences in health care infrastructures, regulatory environments, and AE reporting practices that shape pharmacovigilance data composition, rather than reflecting true differences in underlying risk.[31] These disparities may influence reporting behaviour through variations in professional fluoride application practices, preventive care delivery models, and population-level engagement with safety reporting systems, instead of indicating differential biological effects across regions.[32] A consistent female predominance (FAERS: 53.59%; VigiBase: 57.89%) and elevated reporting in adults aged 18 to 44 years represent reproducible demographic patterns observed across two independent surveillance systems, which should be interpreted as reporting characteristics rather than evidence of higher susceptibility to fluoride-related AEs.[33] Such demographic differences are well recognised in spontaneous reporting databases and may reflect differential health care utilisation, exposure contexts, and reporting propensities across population subgroups.[34] Reporter-type stratification further demonstrated systematic variation in report content, with health care professionals predominantly recording objectively verifiable reactions, such as application-site burns and oral mucosal exfoliation, whereas consumer reports more frequently captured subjective symptoms, including taste disturbance and oral discomfort, highlighting differences in report content rather than event severity.[35] These population-specific patterns underscore the importance of contextualising pharmacovigilance findings within the structural characteristics of surveillance systems and support cautious interpretation of demographic differences observed in spontaneous reporting data.[36] Future studies using dedicated epidemiologic designs will be required to further explore these observations beyond the scope of spontaneous reporting systems.[37]

It is important to note that disproportionality metrics such as the ROR quantify statistical over-reporting within spontaneous reporting systems rather than clinical risk magnitude. In this study, some signals combined elevated ROR estimates with moderate-to-high numbers of reports, whereas others displayed very large ROR values derived from only a few cases. This variability reflects the known sensitivity of disproportionality measures to sparse data and underlying contingency table structure. Accordingly, ROR estimates should be interpreted alongside report frequency and confidence interval width. Signals supported by larger numbers of reports may offer greater statistical stability, whereas those based on very small numerators should be regarded as hypothesis-generating observations requiring confirmation in independent datasets or analytic study designs.

Building upon the demographic foundations, SOC analysis revealed that sodium fluoride AEs were distributed across multiple SOCs, extending beyond the traditionally recognised oral-restricted profile. Gastrointestinal disorders were the predominant category in FAERS (34.22%, $n = 632$), indicating a high frequency of gastrointestinal-related reports within this surveillance system, rather than reflecting established toxicological mechanisms.[38] Previous literature has described gastrointestinal effects following fluoride exposure; however, such dose–response relationships and biological mechanisms cannot be evaluated within spontaneous reporting data.[39] In VigiBase, skin and subcutaneous tissue disorders accounted for 9.68% ($n = 209$) of reports, with chemical skin burns appearing as a notable reported event in the context of professional use of high-concentration sodium fluoride preparations, representing reported exposure scenarios rather than mechanistic injury pathways.[40] Although experimental and clinical studies have explored cellular responses to fluoride exposure, these mechanisms fall outside the scope of pharmacovigilance-based signal detection.[41] Reports of skin-related AEs in dental professionals have been documented in the literature; however, occupational prevalence estimates

cannot be inferred from spontaneous reporting systems.[42] Nervous system disorders mainly involved sensory disturbances such as ageusia and glossodynia, representing recurrent symptom-based PTs reported within surveillance databases, without permitting inference regarding neurotoxicity or neurodevelopmental outcomes.[43] Associations reported in epidemiologic or toxicologic studies of chronic fluoride exposure cannot be assessed using the present study design.[44] Collectively, these findings illustrate the breadth of SOC-level AE reporting associated with sodium fluoride exposure in real-world pharmacovigilance systems, without implying clinical incidence, systemic toxicity, or concentration-dependent biological effects.

PT-level analysis identified recurrent dental-related AE terms with strong disproportionality signals across the two pharmacovigilance databases, indicating a consistent reporting profile for sodium fluoride-associated oral manifestations. In FAERS, tooth discolouration exhibited a strong signal (ROR = 680.45), reflecting frequent co-reporting of this PT in association with sodium fluoride within a spontaneous reporting system, particularly in reports involving professional dental use.[45] Although several reports referenced prescription-strength fluoride formulations, spontaneous reporting data do not permit quantitative assessment of formulation concentration or exposure level, and such associations should therefore be interpreted descriptively. Experimental and clinical dental research has previously demonstrated fluoride-enamel interactions, including binding to enamel matrix components and alterations in enamel surface characteristics, providing a biological context for the repeated reporting of tooth discolouration without implying causality or permanence based on disproportionality findings alone.[46] In VigiBase, dental fluorosis presented with an exceptionally high signal (ROR = 14,383), consistent with its well-established recognition as a fluoride-associated dental outcome within international surveillance systems, particularly in reports involving paediatric populations.[47] The prominence of fluorosis as a high-ranking PT in VigiBase likely reflects cumulative reporting patterns and long-standing diagnostic awareness, rather than direct inference of exposure duration, dose, or critical developmental thresholds.[48] Accordingly, while prior epidemiologic studies have explored dose–response relationships for fluoride exposure and fluorosis, such quantitative associations cannot be derived from spontaneous reporting data, and the present findings should be interpreted as descriptive of disproportionate reporting patterns rather than guidance for clinical dosing or age-specific fluoride selection.[49]

The temporal analysis of AEs provides insight into the reporting timing characteristics of sodium fluoride-associated events within spontaneous reporting systems, rather than directly reflecting the acute toxicity profile of sodium fluoride. Analysis of the FAERS dataset revealed that 78.81% of reported AEs occurred within 30 days of exposure, indicating a predominance of early-reported events following reporter-documented exposure episodes.[50] Time-to-onset estimates in FAERS reflect reporter-documented exposure episodes with identifiable start dates and characterise reporting dynamics of acute or time-defined exposure events, rather than biological latency associated with chronic fluoride exposure. Although this early reporting pattern appears temporally proximate to exposure, spontaneous reporting data do not permit direct inference regarding pharmacokinetic behaviour or toxicodynamic mechanisms, despite existing literature describing rapid systemic absorption of fluoride following oral administration.[51] The high proportion of reports classified as serious AEs (82.87%), when interpreted within the regulatory reporting framework of FAERS, indicates that a substantial fraction of sodium fluoride-associated reports meet seriousness criteria, without providing a standardised measure of clinical severity or outcome probability.[52] Hospitalisation requirements comprised 67.84% of serious FAERS cases, reflecting reported outcome categories rather than direct estimates of health care utilisation or resource burden.[53] External analyses of emergency department data provide contextual information on fluoride poisoning management, but such findings cannot be extrapolated directly from spontaneous reporting systems.[54,55] These temporal patterns describe the concentration of reported events in the early post-exposure period and underscore the importance of contextualising time-to-onset findings within pharmacovigilance datasets, rather than deriving mechanistic conclusions or clinical surveillance protocols from spontaneous reports alone.[56,57]

Building upon the signal detection findings, demographic risk stratification analysis revealed differences in disproportional reporting patterns across sex and age groups, providing context for interpretation of sodium fluoride-associated AE reports within spontaneous reporting systems. ROR-based comparisons showed that female reports accounted for a larger proportion of submissions in both databases, reflecting sex-specific reporting distributions rather than direct evidence of biological susceptibility. Such differences may be influenced by reporting behaviour, health care utilisation patterns, and differential perception of oral symptoms, as suggested in prior pharmacovigilance literature, rather than by intrinsic sensitivity inferred from spontaneous reports alone.[58,59]

Age-stratified analyses further demonstrated variation in the composition of reported PTs across life stages. Paediatric reports accounted for 23.45% of FAERS and 31.68% of VigiBase submissions, with predominant manifestations including acute gastrointestinal symptoms and dental fluorosis, consistent with established recognition of fluoride-related dental outcomes in paediatric reporting contexts.[60] Although developmental and physiologic factors have been discussed in the literature, spontaneous reporting data do not permit quantitative assessment of age-dependent metabolism, exposure, or dose–response relationships, and such interpretations should therefore be approached cautiously.[61,62] Reports from young adults (18-44 years) were characterised by higher representation of dental and aesthetic-related PTs, such as tooth discolouration, potentially reflecting differences in symptom awareness and reporting priorities across age groups.[63] In older adults (≥65 years), reported PTs more frequently involved functional oral complaints, including dysphagia and xerostomia, aligning with age-related oral health conditions commonly captured in pharmacovigilance reports, rather than indicating altered toxicokinetic or increased biological risk.[64] Overall, these stratified findings

describe heterogeneity in reporting patterns across demographic groups and should not be interpreted as evidence of differential susceptibility or risk without confirmation from dedicated epidemiologic studies.[65]

The comparative analysis of the FAERS and VigiBase databases revealed complementary reporting characteristics that facilitated cross-database validation of sodium fluoride-associated safety signals. This dual-database framework illustrates how independent reporting systems, with differing reporting sources and health care contexts, can provide broader perspectives on adverse event reporting patterns when analysed in parallel.[66] FAERS reports more frequently included acute, short-latency presentations, such as chemical gastrointestinal burns, oral mucosal exfoliation, and tooth discolouration, reflecting the prominence of early-reported events within this database.[67] Such patterns were commonly observed in consumer-submitted reports, consistent with prior observations that spontaneous patient reporting often emphasises rapidly perceived oral discomfort and acute symptoms.[68] In contrast, VigiBase reports more prominently captured longer-term and developmental dental outcomes, as exemplified by the markedly elevated disproportionality estimate for dental fluorosis, compared with a lower relative ranking in FAERS. This difference likely reflects variations in reporting composition and documentation practices, including greater representation of professionally submitted reports within VigiBase.[69,70] Reporter source stratification further demonstrated qualitative differences in reporting emphasis, with physician-submitted reports focusing on objectively documented clinical findings, whereas consumer reports more frequently described subjective symptoms such as pain intensity and aesthetic concerns.[71] Cross-database signal intersection identified 122 shared PT-level signals, of which 62% (n = 76) involved oral-related events, indicating consistent recognition of oral manifestations across independent surveillance systems.[72,73] Database-specific signals further illustrated differences in reporting scope, with FAERS-exclusive signals more frequently involving acute hypersensitivity presentations and VigiBase-specific signals more often relating to skeletal or dental developmental outcomes.[74] Differences in report completeness and narrative detail between professional and consumer submissions reflect distinct reporting behaviours rather than differences in signal validity, with each contributing complementary information relevant to pharmacovigilance interpretation.[75]

This study acknowledges several methodological limitations inherent to spontaneous reporting systems that should be considered when interpreting the findings. Underreporting represents a primary constraint, as only a small proportion of AEs are typically submitted to pharmacovigilance databases, particularly for mild or expected reactions, which may lead to disproportionate representation of serious or unusual events without reflecting true clinical incidence.[76,77] The observational nature of spontaneous reporting systems precludes establishment of definitive causality, and the present analyses therefore describe statistical associations and disproportional reporting patterns rather than causal relationships.[78] Extremely high ROR values derived from sparse data were retained when cross-validated across databases; however, such estimates should be interpreted as low-stability, hypothesis-generating signals rather than robust effect sizes.[21] In addition, the absence of exposure population denominators limits its absolute risk estimation, restricting interpretation to relative disproportionality comparisons within reporting datasets,[79] while missing demographic information in both FAERS and VigiBase may further reduce the precision of stratified analyses.[80] Despite these constraints, the dual-database design and cross-database validation provide a consistent and contextualised overview of sodium fluoride-associated reporting patterns, reducing database-specific bias and strengthening interpretability of recurrent signals.[81,82] Within this framework, the identification of 122 validated signals offers a quantitative basis for refining clinical awareness of fluoride-related adverse event profiles and supports the consideration of individualised risk assessment approaches that integrate demographic characteristics, exposure context, and patient-specific oral conditions.[83,84] While spontaneous reporting data cannot inform precise dosing thresholds or exposure–response relationships, the observed concentration- and time-associated reporting patterns underscore the importance of careful formulation selection, appropriate soft tissue protection, and early postapplication monitoring in professional fluoride use.[85,86] Collectively, these findings provide a structured reference for future pharmacoepidemiologic investigations and contribute to the optimisation of fluoride-based preventive and therapeutic practices while maintaining clinical efficacy and patient safety.

Conclusion

This dual-database pharmacovigilance study provides a comprehensive global overview of sodium fluoride safety through the identification and cross-validation of 122 consistent safety signals across international surveillance systems. Oral and dental manifestations constituted the majority of overlapping signals, reflecting the predominant reporting profile observed for sodium fluoride within spontaneous reporting databases. The early temporal clustering of reported events highlights the importance of heightened clinical awareness during the initial period following fluoride exposure. Stratified analyses by demographic and clinical characteristics further demonstrated heterogeneity in reporting patterns across age groups and sexes. Collectively, these findings offer a data-driven reference for strengthening fluoride safety surveillance and support the implementation of context-aware monitoring approaches that consider patient demographics, exposure settings, and timing of use in contemporary dental practice.

Clinical trial number

not applicable.

Ethics statement

This study utilised publicly available, de-identified data from the WHO VigiAccess and FDA FAERS databases. In accordance with international ethical standards for pharmacovigilance research involving anonymised aggregate data, institutional review board approval was not required.

Author contributions

Contributed to conceptualisation, methodology, data curation, formal analysis, and writing original draft, review, and editing: Ning.

Responsible for data validation, statistical analysis, visualisation, and manuscript review. S.L. assisted with data processing, quality control, and review: Huang.

Contributed to the literature review, data interpretation, and editing: Jiang.

Provided methodological guidance, international academic input, and manuscript review: Reissmann, Kreher.

Contributed to methodology validation, offered an international perspective, and participated in review and editing: Schmalz

Supervised the study, contributed to conceptualisation, and participated in review and editing: Chen.

Led project administration and supervision, contributed to conceptualisation and review, and gave final approval of the manuscript: Huang.

Read and approved the final version of the manuscript: All authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT (OpenAI) to refine grammar and improve language readability. After using this tool, the authors manually reviewed, edited, and verified all content to ensure scientific accuracy and academic integrity. The authors take full responsibility for the final content of this work.

Conflict of interest

None disclosed.

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Data availability

All data analysed in this study are publicly accessible from the FDA FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) and the WHO VigiAccess platform (https://www.vigiaccess.org/). The processed datasets supporting the findings of this study are provided within the article and its Supplementary Materials. Further details are available from the corresponding authors upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.identj.2026.109423.

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