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# ASSESSING ASSOCIATIONS BETWEEN REPORT CHARACTERISTICS AND SERIOUS ADVERSE EVENT REPORTING ACROSS MULTINATIONAL DRUG PHARMACOVIGILANCE SUBMISSIONS

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**Abstract:**

This analysis examines how reporting composition shapes the interpretation of serious adverse events in multinational pharmacovigilance surveillance. Public FDA Adverse Event Reporting System data covering 2010 to 2023 provide 140 annual groups representing 13,526,392 reports. Descriptive analysis combines pooled proportions, temporal comparisons, and sex contrasts matched by year and reporter qualification. Female reports account for more submissions, but male reports have a serious reporting percentage 11.76 percentage points higher. This direction persists in 65 of 70 matched comparisons, with all reversals concentrated among lawyer reports. Serious reporting percentages range from 43.28 among consumer reports to 94.60 among lawyer reports. Annual report volume increases while the endpoint serious percentage declines, reflecting faster growth in nonserious submissions. Unequal group volumes also produce a substantial difference between pooled and unweighted summaries. These findings refine the selective reporting perspective by distinguishing recurrent aggregate patterns from reporting channel heterogeneity. International surveillance practice should pair counts with explicit denominators and stratified comparisons to avoid interpreting submission patterns as clinical risk.

**Key Words:** Adverse Event Reporting; Descriptive Analysis; Pharmacovigilance; Reporting Heterogeneity; Sex Differences

## 1. Introduction:

Pharmacovigilance can misrepresent patterns of suspected harm when reporting volume is interpreted without considering the composition of submitted reports. A population group may generate more submissions while another has a greater proportion classified as serious. Reporting channels can also differ in the events they capture, making pooled summaries sensitive to who reports and how reporting changes over time. These distinctions matter for surveillance teams deciding which patterns require further clinical assessment. Sakaeda et al., 2013, describe the FDA Adverse Event Reporting System as a resource for identifying statistical associations from submitted reports rather than establishing drug causation. Alatawi and Hansen, 2017, further demonstrate that underreporting varies across drugs and adverse events, limiting the interpretation of report counts as measures of underlying clinical risk. Patient sex provides an important example of the distinction between reporting frequency and seriousness composition. Biological differences can influence drug exposure and adverse responses, while treatment patterns and reporting decisions can influence which experiences enter surveillance. Zucker and Prendergast, 2020, linked sex differences in pharmacokinetics to differences in adverse drug reactions, particularly greater drug exposure among women for many medicines examined. However, greater susceptibility to particular reactions does not necessarily imply a higher serious reporting proportion across all submitted reports. Watson et al., 2019, found that women accounted for more reports in VigiBase, whereas serious and fatal reports represented higher proportions among men. This evidence establishes that reporting volume and seriousness composition can diverge, but it does not determine whether the same contrast persists within individual reporter categories across successive years in multinational FAERS submissions.

Reporter qualification introduces a second source of variation because reporting depends on opportunities to observe events, interpret their relevance, and submit information. Physicians, pharmacists, other health professionals, lawyers, and consumers occupy different positions in this process. Their reports may therefore differ in composition without implying a corresponding hierarchy of accuracy or clinical importance. Inch et al., 2012, identified both similarities and differences between patient and professional reporting, including similar serious reporting proportions within the comparative studies reviewed. Inácio et al., 2017, showed that patient reports provide information that complements professional submissions. Together, these findings support a selective reporting perspective: observed surveillance patterns reflect the experiences reported and the channels through which they become visible. Reporter qualification consequently warrants examination as a categorical reporting characteristic rather than an ordinal measure of expertise. Reporting year adds a temporal dimension to this selection

process. Changes in the balance of serious and nonserious submissions can alter the pooled serious percentage even when both counts increase. Calendar variation cannot, however, be assigned automatically to stronger surveillance, changing clinical risk, or regulatory communication. Hoffman et al., 2014, found that FDA alerts did not consistently stimulate reporting across the products examined. Measurement also requires separating seriousness from documentation quality. Bergvall et al., 2014, demonstrated variation in report completeness across countries and reporter groups, showing that the presence of a submission does not establish the amount of clinically useful information it contains. These distinctions motivate an outcome defined narrowly as the proportion of eligible submitted reports classified as serious.

The reviewed evidence does not establish whether the pooled sex contrast in multinational FAERS reporting maintains its direction across combinations of reporter qualification and calendar year. Watson et al., 2019, establish the broader sex pattern in a different global repository, while Inch et al., 2012, synthesize comparisons between patient and professional reporting schemes. The present analysis addresses a more specific descriptive question by jointly organizing seriousness counts across sex, reporter qualification, and time. Its contribution is to distinguish a recurrent pooled pattern from variation within reporting strata, while showing how unequal group volumes influence aggregation. This contribution concerns the interpretation of reporting composition rather than the identification of biological mechanisms or causal effects. This study aims to characterize differences in serious adverse event reporting proportions by patient sex, reporter qualification, and reporting year in multinational FAERS submissions from 2010 to 2023. The central research question is how these reporting proportions vary across the three observed dimensions and whether pooled sex differences persist within comparable reporting groups. The analysis draws on 140 annual groups representing 13,526,392 reports, with serious and nonserious counts retained separately. It calculates pooled proportions, describes annual variation, and compares male and female percentages within matched year and reporter categories. The design enables transparent comparisons using consistent denominators without treating aggregate groups as individual patients.

The findings contribute by showing that the higher serious reporting percentage among male reports recurs across most matched comparisons, while reversals are concentrated among lawyer reports. They also demonstrate that an unweighted average of group percentages can differ substantially from the percentage obtained by pooling report counts. These results qualify interpretations based on a single aggregate summary and support presenting report volume alongside seriousness composition and stratified comparisons. The transferable insight is methodological: international surveillance comparisons require attention to reporting categories, observation periods, and denominator construction. The empirical percentages remain specific to the retained multinational FAERS reporting frame.

**2. Theory Conceptual Framework and Research Questions Development:**

This analysis adopts a selective reporting perspective to explain how patient characteristics, reporter roles, and reporting time relate to the composition of pharmacovigilance submissions. An adverse event enters a surveillance database through a sequence of recognition, interpretation, documentation, and submission. Patients, healthcare professionals, manufacturers, and regulators contribute at different stages of this process. Their interactions determine which events become visible to surveillance. Sakaeda et al., 2013, describe the FDA Adverse Event Reporting System as a repository that combines reports from several sources and supports the identification of statistical associations. The conceptual implication is that observed reporting patterns reflect both adverse experiences and the processes through which those experiences enter the database. The focal outcome is the serious adverse event reporting proportion, defined as serious reports divided by all reports with recorded seriousness within each analytical group. This proportion measures the composition of submitted reports rather than the probability that a medicine user experiences harm. Alatawi and Hansen, 2017, found that underreporting varied across drugs and adverse events, demonstrating that reporting systems capture an uneven share of underlying experiences. Consequently, a higher serious reporting proportion may reflect more serious events, less reporting of nonserious events, or both. This analysis therefore examines conditional associations without interpreting them as causal effects on patient safety.

Patient sex identifies the recorded male or female category in the report. Its conceptual relationship with serious reporting involves two processes. Biological differences may influence drug exposure and adverse responses, while differences in treatment, symptom recognition, and reporting may influence which experiences enter surveillance. These processes need not produce the same pattern. Greater susceptibility to some adverse reactions does not necessarily imply a higher proportion of serious reports. Zucker and Prendergast, 2020, linked differences in pharmacokinetics to differences in adverse drug reactions, particularly elevated drug exposure among women. Their findings support a biological explanation for variation in adverse reactions but do not establish a universal direction for serious reporting proportions. The present dataset contains recorded sex and seriousness, allowing comparisons of reporting composition without treating pharmacokinetic mechanisms as measured explanatory variables.

Evidence from global pharmacovigilance further distinguishes reporting frequency from seriousness. Watson et al., 2019, found that women accounted for more adverse reaction reports, whereas serious and fatal reports represented higher proportions among male reports. This distinction makes a simple expectation based on total reporting volume insufficient. This analysis therefore evaluates whether sex differences remain after accounting for reporter qualification and reporting year, without assuming that patterns from another database necessarily apply to multinational FAERS submissions.

RQ1: Does the serious adverse event reporting proportion differ between male and female reports after accounting for reporter qualification and reporting year?

Reporter qualification captures the position of the individual who submits the report. The available categories distinguish physicians, pharmacists, other health professionals, lawyers, and consumers or other individuals without a health profession. These categories represent different opportunities to observe events and different reasons for reporting them. Clinical responsibilities may direct attention toward medically consequential outcomes, whereas direct experience may draw attention toward symptoms and disruptions that clinical documentation captures less readily. Neither process establishes a fixed ranking of seriousness across all reporter categories. Professional knowledge also interacts with organizational constraints. Reporting requires time, access to information, and confidence that an event warrants submission. Stergiopoulos et al., 2016, identified uncertainty about causation, limited time, and fragmented information systems as barriers to reporting among healthcare professionals. García Abeijon et al., 2023, likewise identified knowledge and attitudes as factors associated with underreporting. These findings support the expectation that reporter categories capture different reporting processes, although the underlying barriers are not directly measured in the available dataset. Differences in reporting processes do not necessarily imply differences in serious reporting proportions. Inch et al., 2012, found similarities in the proportions of serious reports submitted by patients and healthcare professionals within the studies included in their review, despite differences in other report characteristics. This evidence challenges an assumption that professional reporting consistently concentrates on more serious events. Reporter qualification is therefore treated as a categorical predictor, with differences assessed across categories rather than along an artificial scale of professional authority.

RQ2: Does the serious adverse event reporting proportion differ across reporter qualification categories after accounting for patient sex and reporting year?

Reporting year identifies when the FDA first received a report. Its conceptual relevance concerns changes in the reporting environment over time. Changes in participation, reporting practices, and the composition of submitted cases can alter the balance between serious and nonserious reports. An increase in submissions alone does not determine the direction of this change. The serious reporting proportion rises only when serious reports increase relative to nonserious reports and falls when the reverse occurs. Regulatory communication provides one possible source of temporal variation, but its influence cannot be assumed. Hoffman et al., 2014, found little evidence that FDA alerts consistently increased reporting across the drugs examined. Their findings limit an interpretation in which calendar changes automatically reflect stronger public attention or regulatory stimulation. This analysis uses reporting year to examine temporal association, without attributing that association to specific interventions that the dataset does not identify. The temporal question concerns a linear association over 2010 to 2023 after accounting for sex and reporter qualification. Annual proportions also provide a descriptive account of fluctuations that a single linear trend may not capture. A weak linear association would therefore indicate limited evidence of a consistent directional trend rather than an absence of annual variation.

RQ3: Is reporting year linearly associated with the serious adverse event reporting proportion after accounting for patient sex and reporter qualification?

The conceptual framework connects three observed report characteristics to one observed reporting outcome. Patient sex, reporter qualification, and reporting year enter as separate predictors rather than indicators of a latent construct or components of a composite score. The dataset contains 140 groups defined by year, sex, and reporter qualification, with serious and nonserious counts retained for each group. These counts support grouped binomial analysis of the three research questions. Each relationship represents an association conditional on the other measured predictors. The framework concerns multinational submissions within one reporting repository and does not represent comparisons between national surveillance systems. The questions permit differences, no detectable differences, and inconclusive evidence without redefining the expected relationships after examining results.

## 3. Data:

This analysis documents the provenance, selection, and measurement of multinational pharmacovigilance reports received from 2010 to 2023. It consolidates verified aggregate counts into comparable reporting groups and uses explicit denominators to describe differences in serious adverse event reporting.

### 3.1 Data Sources, Population, and Sample Construction:

FAERS receives reports concerning suspected adverse events and medication errors through several reporting channels. Sakaeda et al., 2013, describe its role in surveillance and distinguish reported associations from established drug effects. The supplied workbook preserves the extraction queries,

retrieval metadata, and source update information. These metadata distinguish the extraction snapshot from the observation period. The extract represents historical reports available in that snapshot rather than information frozen at each original reporting date. The observation window extends from 1 January 2010 to 31 December 2023. Calendar year follows receivedate, the date the FDA first received the report. Geographical coverage includes multinational submissions available through FAERS, without restricting reporter country. Sectoral coverage encompasses drug adverse event reporting across the products represented in the source. This setting differs from analyses restricted to domestic serious reports, such as Sonawane et al., 2018, and does not constitute a comparison between national pharmacovigilance systems.

The target population comprises drug adverse event reports within the multinational reporting setting and observation window. The accessible sampling frame comprises publicly available FAERS records with recorded male or female sex, one of five specified reporter qualifications, and serious or nonserious status. Selection applied these restrictions directly in the extraction queries and did not involve random sampling. Records with unknown or missing sex, reporter qualification, or seriousness fall outside the extract. Their separate exclusion counts cannot be recovered from the supplied aggregate tables. Underreporting also separates the accessible frame from underlying adverse experiences among medicine users, as demonstrated by Alatawi and Hansen, 2017. The unit of analysis is a group defined by calendar year, patient sex, and reporter qualification. Two sex categories and five reporter categories produce ten recurring reporting strata. Each stratum appears in all fourteen years, yielding a balanced aggregate structure of 140 observations. These observations describe successive annual collections of reports rather than repeated measurements of the same patients. Counts represent annual receipt flows classified by seriousness as recorded in the extraction snapshot. Watson et al., 2019, demonstrate why report volume and the proportion classified as serious require separate interpretation.

Table 1: Sample construction

| Stage | Reporting Strata | Aggregate Observations | Reports Represented | Rule or Verification |
|---|---|---|---|---|
| Eligible extracted source counts | 10 | 280 | 13,526,392 | Fourteen years, two sex categories, five reporter categories, and two seriousness categories |
| Consolidation by analytical key | 10 | 140 | 13,526,392 | Serious and nonserious counts combined within year, sex, and reporter qualification |
| Removal of duplicate analytical keys | 0 removed | 0 removed | 0 removed | No duplicate analytical keys identified |
| Removal for missing retained analytical fields | 0 removed | 0 removed | 0 removed | All retained groups have complete counts and classifications |
| Final descriptive sample | 10 | 140 | 13,526,392 | All consolidated groups retained |

The final sample contains 7,715,957 serious reports and 5,810,435 nonserious reports. Eligibility restrictions were embedded in the extraction queries. The workbook does not establish a separate protocol registration date or document subsequent changes to these restrictions. The openFDA licensing statement makes its data generally available under a CC0 public domain dedication, subject to service terms and stated exceptions. U.S. Food and Drug Administration, 2014, provides the applicable licensing information.

**3.2 Data Integration, Cleaning, and Quality Assurance:**

Integration combined count responses from one source rather than merging independent datasets. The analytical key consists of reporting year, patient sex code, and reporter qualification code. Serious and nonserious count series were matched using this key, producing one row for each reporting group. All 140 groups contained both counts, with no unmatched groups or unexpected increase in observations. Banda et al., 2016, show that FAERS preparation choices can affect results. The present construction therefore preserves original counts separately from calculated totals and proportions. Identifier harmonization assigned readable labels to existing sex and reporter qualification codes. No drug name mapping or product classification was required because the extraction pooled products rather than estimating product comparisons. Rahman et al., 2017, document methodological difficulties in comparisons between product categories, reinforcing the distinction between reporting group analysis and analyses requiring product identity harmonization.

Quality checks verified unique analytical keys, complete coverage across fourteen years, nonnegative integer counts, positive denominators, and proportions bounded between zero and one. Every serious and nonserious count in the analytical table matched its corresponding source count. Every total equalled the sum of its components, and every stored outcome proportion matched the reconstructed

ratio. These checks identified no inconsistencies in the retained data. The absence of duplicate aggregate keys does not establish the absence of duplicate patient reports in FAERS. Individual report identifiers and clinical narratives were not included in the extract, so independent patient level deduplication was not performed. Tregunno et al., 2014, demonstrate that duplicate detection requires information beyond aggregate count tables. Reported totals therefore refer to source reports rather than verified unique patients or unique adverse events.

No retained analytical field was missing. This completeness partly reflects extraction restrictions and does not imply complete source reporting. No imputation, interpolation, substitution of missing values with zero, or external matching was performed. García Abeijon et al., 2023, identify knowledge and reporting attitudes as contributors to underreporting, indicating that complete extracted fields cannot remove selection occurring before submission. Calendar alignment used first receipt year consistently across groups. Counts required no currency conversion, inflation adjustment, or frequency conversion. All positive counts and proportions were retained without trimming or winsorization. The historical snapshot may incorporate report updates and does not reconstruct information available contemporaneously. Annual changes describe reporting composition and cannot identify the effects of particular regulatory communications. Hoffman et al., 2014, found that alerts did not consistently increase reporting across the products examined, supporting caution against attributing calendar variation to a single reporting mechanism.

**3.3 Variable Measurement, Construction, and Validation:**

The dependent variable is the serious adverse event reporting proportion. It measures the share of retained reports classified as serious within each reporting group. Classification follows the source field serious rather than independent adjudication of clinical records. The analysis retains the term adverse event because reporting alongside medicine use does not establish a drug reaction. Aronson, 2013, explains the distinctions between adverse effects, reactions, and their clinical manifestations. Equation 1 constructs the group denominator.

$$N_g = S_g + U_g$$

Here, $N_g$ denotes total retained reports in group g, $S_g$ denotes reports coded serious, and $U_g$denotes reports coded nonserious. Group gis defined by reporting year, patient sex, and reporter qualification. Equation 2 constructs the dependent variable.

$$p_g = \frac{S_g}{N_g}$$

Here, $p_g$ denotes the serious reporting proportion for group g, using the counts defined in Equation 1. The stored ratio ranges from zero to one. Multiplication by 100 expresses the measure as a percentage. A higher value indicates a greater serious share among submitted reports rather than a higher incidence of harm among medicine users. Patient sex, reporter qualification, and reporting year are observed explanatory dimensions. Recorded sex distinguishes male from female reports and does not measure pharmacokinetics, treatment exposure, or biological susceptibility. Zucker and Prendergast, 2020, provide evidence of pharmacokinetic differences relevant to adverse reactions, but these mechanisms cannot be measured through the recorded sex field alone.

Reporter qualification distinguishes physicians, pharmacists, other health professionals, lawyers, and consumers or other individuals without a health profession. Numerical codes identify categories rather than increasing levels of expertise or seriousness. Inch et al., 2012, document similarities and differences between patient and professional reports, while Stergiopoulos et al., 2016, identify variation in professional reporting processes. These findings support separate category descriptions rather than combining reporter codes into a continuous score.

Table 2: Variable dictionary

| Variable or Indicator | Analytical Role | Definition and Construction | Source and Identifier | Unit and Frequency | Transformation and Direction | Missing Value Rule | Coverage and Limitation |
|---|---|---|---|---|---|---|---|
| Reporting year | Observed explanatory dimension | Calendar year of first FDA receipt | FAERS, receive date | Year, annual | Original year retained | Outside window excluded | 2010 to 2023; does not necessarily identify event onset |
| Patient sex | Observed explanatory dimension | Code 1 male and code 2 female | FAERS, patient. patientsex | Category, annual grouping | Labels assigned; no ordinal interpretation | Unknown and missing categories excluded during extraction | Complete in 140 groups; limited to recorded categories |
| Reporter qualification | Observed explanatory dimension | Codes 1 to 5 identify the five retained reporter categories | FAERS, primary source. qualification | Category, annual grouping | Labels assigned; no ranking imposed | Unspecified and missing categories excluded during extraction | Complete in 140 groups; does not measure report quality |
| Serious reports | Outcome numerator | Count of reports with serious code | FAERS, serious | Reports, annual | Original count retained | No missing retained counts | 140 groups; not independently |

| Variable or Indicator | Analytical Role | Definition and Construction | Source and Identifier | Unit and Frequency | Transformation and Direction | Missing Value Rule | Coverage and Limitation |
|---|---|---|---|---|---|---|---|
| | | 1 | | | | | adjudicated |
| Nonserious reports | Denominator component | Count of reports with serious code 2 | FAERS, serious | Reports, annual | Original count retained | No missing retained counts | 140 groups; not a population without adverse events |
| Total reports | Denominator | Serious plus nonserious reports | Constructed from FAERS counts | Reports, annual | Equation 1 | Requires both components | Positive in every retained group |
| Serious reporting proportion | Dependent variable | Serious reports divided by total reports | Constructed from FAERS counts | Ratio, annual | Equation 2; higher values indicate a larger serious share | Undefined if denominator is zero; no such case occurred | 140 groups; conditional on submission and eligibility |
| Year since 2010 | Derived time coding | Reporting year minus 2010 | Constructed from receive date | Years, annual | Values from zero to thirteen | No missing retained values | Equivalent time ordering; not an additional construct |

Table 3 reports descriptive statistics across the 140 analytical groups. Standard deviations describe variation between groups rather than sampling uncertainty.

Table 3: Descriptive statistics across reporting groups

| Measure | Valid Groups | Mean | Standard Deviation | Median | Minimum | Maximum |
|---|---|---|---|---|---|---|
| Serious reports | 140 | 55,113.98 | 41,798.55 | 53,632.50 | 1,484 | 178,417 |
| Nonserious reports | 140 | 41,503.11 | 57,341.92 | 20,703.50 | 55 | 268,290 |
| Total reports | 140 | 96,617.09 | 93,841.55 | 70,539.00 | 1,941 | 383,130 |
| Serious reporting percentage | 140 | 68.43 | 17.09 | 70.68 | 29.97 | 99.38 |

The mean group percentage assigns equal weight to every reporting group. It differs from the pooled serious reporting percentage of 57.04 because groups have unequal report volumes. Measurement validation consists of source reconciliation and arithmetic consistency checks. The variables are observed categories and count based ratios, so no latent measurement model is imposed. Montastruc et al., 2011, emphasize that measures derived from spontaneous reports require interpretation within their reporting denominators.

**3.4 Analytical Framework, Identification, and Reproducibility:**

The implemented analysis is descriptive. It summarizes serious reporting composition by recorded sex, reporter qualification, and calendar year. Its estimand is the proportion of serious reports among eligible submitted reports within a specified group. This differs from a drug specific disproportionality measure or a population incidence rate. Faillie, 2019, explains the comparison structure required for reporting odds ratios; the present denominator instead combines serious and nonserious reports within the same reporting group. Equation 3 defines the pooled proportion used for summaries across several groups.

$$P_A = \frac{\sum_{g \in A} S_g}{\sum_{g \in A} N_g}$$

Here, A denotes the set of groups included in a summary, $P_A$ denotes their pooled serious reporting proportion, and $S_g$ and $N_g$ retain their definitions from Equation 1. Pooling by sex combines all years and reporter categories for that sex. Pooling by reporter qualification or year follows the same denominator rule. This construction weights each group by its report count rather than averaging percentages without regard to group size. Differences between pooled percentages are expressed in percentage points. They describe contrasts within the retained reporting frame rather than adjusted effects or differences in clinical risk. Interpretation emphasizes observed magnitude and denominator composition rather than significance labels, consistent with Greenland et al., 2016, and Wasserstein and Lazar, 2016.

The data do not identify causal effects of sex, reporter role, or calendar time. Reporting selection, product composition, underlying patient characteristics, and residual duplicate reports may influence observed contrasts. The extract does not contain the information required to separate these processes. Hernán, 2018, stresses that analytical claims must correspond to the scientific objective and identification strategy; the present objective remains description of submitted reports. Reproducibility rests on the retained source count table, exact extraction URLs, category definitions, and editable construction formulas. Verification matched all 280 source counts to the 140 analytical rows and reconstructed every denominator and proportion. The workbook preserves these relationships without replacing original counts. This traceable calculation sequence accords with the computational reproducibility principles discussed by Sandve et al., 2013. Live queries may return revised counts, so reproducing the supplied results requires the retained extraction snapshot alongside the query definitions.

## 4. Methods:

### 4.1 Research Design and Scope of Interpretation:

This analysis uses a retrospective descriptive design to examine serious adverse event reporting across patient sex, reporter qualification, and calendar year. The analytical unit is a group defined by these three classifications. The dataset contains 140 groups covering multinational FAERS submissions received from 2010 to 2023. The sample construction and measurement definitions appear in Tables 1 and 2. The principal quantity of interest is the proportion of retained reports classified as serious within a specified reporting group. Comparisons examine differences between sex categories, variation across reporter qualifications, and changes in annual reporting composition. This design distinguishes the number of submitted reports from the concentration of serious reports within those submissions. Useful variation arises across reporting categories and calendar years. Matching male and female groups within the same reporter category and year provides a more specific comparison than pooling all submissions. It holds these two classifications constant descriptively but does not adjust for differences in medicines, age, underlying conditions, or exposure. Consequently, matched contrasts describe reporting composition rather than causal effects or differences in population clinical risk. Alatawi and Hansen, 2017, demonstrate that reporting completeness varies across drugs and adverse events, supporting this restricted interpretation.

### 4.2 Analytical Specification and Comparative Calculations:

The analysis calculates group totals and serious reporting proportions using Equations 1 and 2. Equation 3 pools counts across selected groups before calculating the corresponding proportion. Pooling separately by sex, reporter qualification, and year produces the summaries presented in Tables 4 to 6. These classifications represent alternative views of the same reports rather than independent samples. Sex comparisons use percentage point differences. Equation 4 defines the contrast within each matched year and reporter category.

$$\Delta_{rt} = 100[p_{Mrt} - p_{Frt}]$$

Here, $\Delta_{rt}$ denotes the male percentage minus the female percentage within reporter category r and reporting year t. The terms $p_{Mrt}$ and $p_{Frt}$ denote the corresponding serious reporting proportions calculated using Equation 2. Reporter category rtakes five categorical values, and year tcovers 2010 to 2023. Positive contrasts indicate a higher serious reporting percentage among male reports; negative contrasts indicate a higher percentage among female reports. The matching procedure generates 70 comparisons. The analysis records their direction, summarizes the minimum and maximum contrasts, and examines whether reversals concentrate within particular reporter categories. These comparisons supplement the pooled category summaries and are interpreted as descriptive stratification rather than interaction estimates. Distributional summaries include the arithmetic mean, median, minimum, maximum, and sample standard deviation across the 140 groups. Each group receives equal weight in these summaries. In contrast, Equation 3 weights group proportions by their report denominators. Presenting both summaries distinguishes the distribution across reporting groups from the composition of all retained submissions. Endpoint changes in report count use Equation 5.

$$G_X = 100\left[\frac{X_{2023}}{X_{2010}} - 1\right]$$

Here, $G_X$ denotes the percentage change in an annual count between the endpoint years. The quantity $X_t$denotes total, serious, or nonserious reports in year t. Changes in serious reporting percentages are calculated by subtraction and expressed in percentage points. This distinction prevents count growth from being confused with changes in reporting composition. The outcome is not a reporting odds ratio for a particular medicine and adverse event combination. Faillie, 2019, describes the comparison structure required for that approach. The present specification instead compares seriousness shares within the retained reporting frame.

### 4.3 Analytical Sample and Processing Procedures:

All calculations use the same 140 groups. The ten recurring combinations of sex and reporter qualification have observations in every year, producing a balanced aggregate structure. This balance concerns reporting categories rather than longitudinal follow up of individual patients. Processing begins with the 280 source count rows. Serious and nonserious counts are matched using reporting year, sex code, and reporter qualification code. Their consolidation produces one row per analytical key. Readable category labels are assigned without changing source classifications. The counts then generate totals, group proportions, pooled summaries, and matched contrasts in that order.

Sex and reporter qualification codes are treated as categorical labels. Their numerical values do not imply increasing seriousness, expertise, or reporting quality. Calendar year follows first FDA receipt rather than event onset. The analysis retains the source seriousness classification and does not independently adjudicate clinical outcomes. No retained analytical field is missing, and no group is lost during consolidation or calculation. Extraction restrictions exclude unspecified or missing source classifications before aggregation. No imputation, interpolation, or replacement of missing values with zero is applied. All observed groups remain in the analysis, including those with extreme reporting percentages. No trimming or winsorization is performed. This sequence preserves original counts separately from derived measures.

Banda et al., 2016, show that FAERS cleaning and normalization decisions can materially affect analytical results. The restricted processing used here therefore maintains a direct relationship between each source count and its contribution to the reported summaries.

**4.4 Verification, Reproducibility, and Interpretive Limits:**

Numerical verification uses Python 3.12.14 and standard library functions for workbook extraction, grouping, arithmetic, and descriptive statistics. The statistics module calculates sample standard deviations using the number of groups minus one as the divisor. Calculations retain numerical precision internally, and reported percentages and contrasts are rounded only for presentation. Verification checks the uniqueness of analytical keys, the presence of all expected category combinations, complete annual coverage, and agreement between source and analytical counts. It also checks that counts are nonnegative integers, every denominator is positive, totals equal their components, and reconstructed proportions agree with the workbook values within an absolute tolerance of $10^{-12}$. All 280 source counts reconcile with their corresponding analytical entries.

The analysis reports descriptive magnitudes without significance tests, standard errors, or confidence intervals. The standard deviations in Table 3 describe variation across reporting groups rather than uncertainty around a population parameter. Interpretation does not depend on classifying differences as statistically significant, consistent with the distinctions emphasized by Greenland et al., 2016. Two implemented comparisons assess the consequences of aggregation. Comparing unweighted group summaries with pooled proportions examines the influence of unequal report volumes. Comparing pooled sex contrasts with contrasts matched by year and reporter qualification examines whether the overall direction conceals variation within reporting groups. These procedures address descriptive consistency and do not establish causal identification.

Unique aggregate keys do not establish unique patients or clinical events. Independent patient level deduplication cannot be performed using the supplied count tables. Tregunno et al., 2014, demonstrate that duplicate detection requires information beyond aggregate reporting classifications. Accordingly, the represented totals remain counts of source reports. The workbook retains source counts, exact query URLs, variable definitions, and editable formulas. These materials document how the reporting groups and principal proportions were constructed. Reproduction requires the retained snapshot because later executions of the same queries may return revised historical counts. The methodological contribution is a transparent application of stratification and denominator consistent aggregation, with claims confined to the reporting patterns these procedures measure.

**5. Findings:**

This analysis examines how serious adverse event reporting varies by patient sex, reporter qualification, and reporting year. The findings distinguish report volume from the proportion classified as serious and assess whether pooled differences persist within reporting groups. All comparisons describe the retained multinational reporting frame from 2010 to 2023. The analytical sample comprises 140 groups representing 13,526,392 reports. Each of the ten combinations of sex and reporter qualification appears in all fourteen years. Serious reports account for 7,715,957 submissions, equivalent to 57.04 percent of the retained total. All analytical groups contain complete counts, and every calculated denominator reconciles with its serious and nonserious components. These totals describe submitted reports rather than unique patients or adverse event incidence. Alatawi and Hansen, 2017, demonstrate that reporting completeness varies across drugs and events, limiting extrapolation from submission counts to underlying clinical risk.

The distribution of reporting proportions shows substantial heterogeneity across analytical groups. The median serious reporting percentage is 70.68, while the unweighted mean is 68.43, with a standard deviation of 17.09 percentage points. Group percentages range from 29.97 to 99.38. The unweighted mean exceeds the pooled percentage by 11.38 percentage points because equal weighting of groups gives relatively small reporting groups more influence than their contribution to total submissions. The pooled percentage therefore provides the appropriate summary of the serious share across all retained reports.

Table 4: Report volume and serious reporting percentage by patient sex and reporter qualification

| Reporting Category | Analytical Groups | Total Reports | Serious Reports | Serious Reporting Percentage |
|---|---|---|---|---|
| All retained reports | 140 | 13,526,392 | 7,715,957 | 57.04 |
| Male | 70 | 5,358,916 | 3,437,534 | 64.15 |
| Female | 70 | 8,167,476 | 4,278,423 | 52.38 |
| Physician | 28 | 3,038,921 | 2,165,148 | 71.25 |
| Pharmacist | 28 | 886,171 | 526,188 | 59.38 |
| Other health professional | 28 | 2,617,447 | 1,814,868 | 69.34 |
| Lawyer | 28 | 364,865 | 345,172 | 94.60 |
| Consumer or other individual without a health profession | 28 | 6,618,988 | 2,864,581 | 43.28 |

Female reports constitute 60.38 percent of retained submissions and exceed male reports in both total volume and the number classified as serious. Nevertheless, the serious reporting percentage is higher among male reports, at 64.15 percent compared with 52.38 percent among female reports. The difference is 11.76 percentage points, calculated before rounding. Greater female reporting volume therefore coexists with a lower serious share. This distinction is consistent with Watson et al., 2019, who identified more reports concerning women but higher proportions of serious and fatal reports concerning men in global pharmacovigilance data.

The pooled sex difference persists when reports are compared separately within each reporter qualification category. Male reporting percentages exceed female percentages by 12.36 percentage points among physicians, 11.50 among other health professionals, 8.74 among consumers or other individuals without a health profession, 8.47 among pharmacists, and 3.42 among lawyers. The variation in magnitude indicates that the overall contrast does not describe every reporting channel equally.

Table 5: Serious reporting percentages by sex within reporter qualification categories

| Reporter Qualification | Male Percentage | Female Percentage | Male Percentage Minus Female Percentage, Percentage Points |
|---|---|---|---|
| Physician | 78.38 | 66.03 | 12.36 |
| Pharmacist | 63.98 | 55.51 | 8.47 |
| Other health professional | 76.15 | 64.65 | 11.50 |
| Lawyer | 96.28 | 92.86 | 3.42 |
| Consumer or other individual without a health profession | 48.83 | 40.09 | 8.74 |

A further descriptive comparison matches male and female reporting percentages within the same year and reporter category. Male percentages are higher in 65 of the 70 matched comparisons. Physicians, pharmacists, other health professionals, and consumers or other individuals without a health profession show this direction in every year. Lawyer reports contain all five reversals, with female percentages exceeding male percentages in those comparisons. Across lawyer comparisons, the male percentage ranges from 10.12 percentage points below the female percentage to 28.35 percentage points above it. The overall sex contrast is therefore recurrent across reporting strata, while its direction is not universal. Reporter qualification also separates reporting volume from seriousness composition. Consumers or other individuals without a health profession account for 48.93 percent of all retained reports but have the lowest serious reporting percentage, at 43.28. Lawyer reports account for 2.70 percent of submissions but have the highest serious percentage, at 94.60. The difference between these categories is 51.32 percentage points. Physician and other health professional reports occupy intermediate positions, with serious percentages of 71.25 and 69.34, respectively. Pharmacist reports have a serious percentage of 59.38.

These contrasts establish differences in submitted report composition rather than a ranking of reporter accuracy or clinical expertise. Reporter categories can differ in the events they encounter and select for submission. Inch et al., 2012, found that comparisons between patient and professional reporting varied across reporting schemes, including similarities in serious reporting proportions within the studies reviewed. The present findings therefore identify the pattern in the retained FAERS extract without treating it as a universal relationship across surveillance systems. Annual results show that reporting volume and the serious share do not move together consistently. Total reports increase from 376,126 in 2010 to 1,123,591 in 2023, an increase of 198.73 percent. Over the same interval, the serious reporting percentage decreases from 63.36 to 56.27, a decline of 7.09 percentage points. Serious report counts increase by 165.30 percent, while nonserious counts increase by 256.51 percent. The lower endpoint percentage therefore reflects faster growth in nonserious submissions rather than a reduction in the number of serious submissions relative to the initial year.

Table 6: Annual report volume and serious reporting percentage

| Reporting Year | Total Reports | Serious Reports | Serious Reporting Percentage |
|---|---|---|---|
| 2010 | 376,126 | 238,296 | 63.36 |
| 2011 | 491,939 | 322,358 | 65.53 |
| 2012 | 625,310 | 410,498 | 65.65 |
| 2013 | 701,678 | 408,627 | 58.24 |
| 2014 | 757,645 | 446,907 | 58.99 |
| 2015 | 1,037,678 | 494,831 | 47.69 |
| 2016 | 1,023,980 | 517,092 | 50.50 |
| 2017 | 1,091,531 | 571,745 | 52.38 |
| 2018 | 1,222,828 | 649,211 | 53.09 |
| 2019 | 1,206,602 | 670,774 | 55.59 |

| Reporting Year | Total Reports | Serious Reports | Serious Reporting Percentage |
|---|---|---|---|
| 2020 | 1,206,745 | 713,362 | 59.11 |
| 2021 | 1,350,448 | 882,683 | 65.36 |
| 2022 | 1,310,291 | 757,364 | 57.80 |
| 2023 | 1,123,591 | 632,209 | 56.27 |

The annual serious percentage follows a changing rather than consistently increasing or decreasing pattern. It reaches 65.65 percent in 2012, falls to 47.69 percent in 2015, and rises in each subsequent year through 2021, when it reaches 65.36 percent. It then declines in both remaining years. The difference between the highest and lowest annual percentages is 17.96 percentage points. A comparison restricted to the first and last years would conceal the intervening decline and recovery. The male serious reporting percentage exceeds the female percentage in every annual pooled comparison. Annual differences range from 9.67 percentage points in 2023 to 14.09 in 2014. This persistence strengthens the descriptive finding that the pooled sex contrast is not confined to a single year. It does not establish a biological explanation, because product composition, patient characteristics, and reporting selection remain embedded in the aggregate counts.

Calendar variation cannot be attributed to a particular regulatory action or change in surveillance performance from these results alone. Hoffman et al., 2014, found that FDA alerts did not consistently stimulate reporting across the products examined. The observed annual pattern consequently supports a conclusion about changing reporting composition rather than a verified explanation of the institutional processes producing that change. Taken together, the findings establish three descriptive conclusions. Male reports have a higher serious share despite lower submission volume, reporter categories differ substantially in seriousness composition, and annual reporting percentages vary without a uniform temporal direction. The matched comparisons show that the sex difference recurs across most year and reporter combinations, with reversals concentrated among lawyer reports. These conclusions apply to the retained source reports. They do not establish adjusted effects, clinical incidence, or unique patient counts. Tregunno et al., 2014, demonstrate that duplicate reports can affect pharmacovigilance evidence; the absence of patient level deduplication therefore limits interpretation of the represented report totals.

**6. Discussion:**

More adverse event reports do not necessarily indicate a greater concentration of serious outcomes. Tables 4 and 5 reveal this distinction through the coexistence of higher female reporting volume and a higher serious reporting percentage among male reports. Equations 1 and 2 separate the number of submissions from their seriousness composition, preventing either measure from substituting for the other. The contribution of this analysis lies in tracing that distinction across sex, reporter qualification, and time within a common reporting frame. Male percentages exceed female percentages in 65 of 70 comparisons matched by year and reporter category, while all five reversals occur among lawyer reports. This pattern adds specificity to the pooled contrast by identifying both its recurrence and its boundary. Harpaz et al., 2012, emphasize the importance of matching pharmacovigilance questions to the information available in reporting databases. Here, stratification reveals a reporting asymmetry that the overall percentage alone conceals, without converting that asymmetry into evidence of biological causation. Reporter qualification helps locate where the observed sex difference varies, but it does not establish a transmission mechanism. Table 5 shows a positive male versus female contrast within every reporter category when counts are pooled across years, although the magnitude differs between categories. The matched annual comparisons further show that four reporter categories maintain the same direction throughout the observation period, whereas lawyer reports contain reversals. Under a selective reporting perspective, this heterogeneity is consistent with reporting channels capturing different combinations of experiences and submission decisions. It does not identify which decisions produced the differences. Caster et al., 2014, demonstrate that report content and quality can contribute information beyond aggregate frequency in safety signal assessment. The present evidence extends the descriptive interpretation by showing where additional case information would matter most: reporting strata whose pooled direction masks variation across years.

The weighting contrast identifies a further distinction between numerical prominence and influence on the pooled outcome. Consumers or other individuals without a health profession contribute almost half of retained submissions but have the lowest serious reporting percentage, while lawyer reports contribute a small share and have the highest percentage, as shown in Table 4. Equation 3 makes the implication explicit: each category contributes to the pooled percentage according to its report volume, rather than its seriousness percentage alone. Consequently, the unweighted mean across groups exceeds the pooled percentage by 11.38 percentage points. This difference is a property of aggregation, not a decomposition of causal effects. It changes the interpretation of surveillance summaries by showing that a typical reporting group and a typical submitted report yield different numerical descriptions. Inácio et al., 2017, identify patient reporting as a complementary source of pharmacovigilance information. The lower serious share in the broad consumer category therefore provides no basis for discounting its contribution; it shows that contribution and seriousness concentration measure different aspects of surveillance evidence. Temporal

variation introduces another constraint on interpreting surveillance growth. Table 6 shows that report volume increases substantially between the endpoints while the serious reporting percentage declines, with an intervening fall and recovery. Equations 1 to 3 explain how this can occur: nonserious submissions increase faster than serious submissions, changing the denominator composition even when serious report counts rise. The resulting pattern cautions against treating either rising volume or a falling serious percentage as a direct indicator of improved safety or reporting performance. A related distinction concerns data quality. Arithmetic consistency across the aggregate tables establishes coherent construction, but it does not establish clinical completeness. Durrieu et al., 2016, found that seriousness and documentation completeness were associated in reports from French general practitioners, while Bergvall et al., 2014, documented variation in completeness across countries and reporter groups. These findings reinforce the need to distinguish seriousness, completeness, and reporting volume rather than treating them as interchangeable measures of system performance.

The international relevance of these findings lies in a transferable interpretation of multinational reporting data rather than a ranking of countries. Tables 4 to 6 show that conclusions depend on whether comparisons concern submission volume, seriousness composition, reporter category, or reporting year. The geographical variation documented in global completeness research and the complementary information identified in patient reporting research make direct comparisons between reporting systems dependent on comparable definitions and denominators. The present analysis contributes a common descriptive structure for making those distinctions visible. Surveillance summaries should therefore present counts alongside serious reporting percentages, retain reporter categories, and examine whether pooled sex differences persist within comparable reporting strata. Equation 3 provides a transparent basis for aggregation, while Table 5 demonstrates why aggregation should be accompanied by stratification. The theoretical refinement is that selective reporting must be considered at the level of reporting groups, because a stable overall contrast can coexist with reversals within a particular channel. This conclusion supports more precise interpretation of international pharmacovigilance evidence without claiming that the observed differences identify clinical risk or surveillance effectiveness.

**7. Conclusion and Implications:**

Global drug safety surveillance depends on interpreting what reports contain, not simply counting how many arrive. This analysis shows that differences in reporting composition persist across most comparable groups, while concentrated reversals reveal boundaries concealed by pooled summaries. Its core contribution is a stratified empirical account that distinguishes reporting volume, seriousness concentration, and aggregation. This distinction refines the selective reporting perspective by demonstrating that a recurrent overall pattern can coexist with contrasting patterns within particular reporting channels. The evidence supports conditional descriptive interpretation rather than causal attribution. For surveillance managers, the implication is to examine comparable reporting groups before allocating clinical review resources or interpreting changes in overall percentages. Reporting dashboards should display counts alongside proportions, preserve category distinctions, and distinguish annual fluctuations from sustained changes. Regulatory institutions can strengthen transparency by standardizing denominator definitions and documenting the scope of pooled comparisons. Operational teams can incorporate these checks into routine surveillance reviews without treating a high serious share as proof of superior reporting quality or greater underlying clinical risk. Across international settings, this approach offers a transferable discipline for comparing surveillance evidence. Its practical value lies in reducing misleading interpretations while preserving diverse reporting contributions to decisions concerning public health protection.

The aggregate structure creates opportunities for extensions using individual reports linked to clinical information and medicine exposure. Such data could distinguish reporting selection from differences in underlying adverse experiences and permit independent duplicate assessment. Comparisons across national repositories could evaluate whether the observed reporting patterns persist under different submission rules and institutional arrangements. Consistent historical snapshots would support analysis of revisions and changing information availability. Future work could also examine treatment composition, age, and documentation completeness within comparable reporting groups. These extensions would assess transferability and investigate mechanisms while retaining the distinction between submitted reports and population clinical risk.

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