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Drug–drug interaction safety reporting and high-multiplicity interacting-drug attribution in South and Southeast Asia: an archived openFDA secondary analysis including Pakistan, 2021– 2025

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Research Article

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Abstract

Introduction:

Although drug–drug interactions are important issues with respect to clinical and pharmacy safety, spontaneous-reporting systems label multiple drugs as interacting but not as a causal drug pair.

Aim

To characterize high-multiplicity interacting-drug attribution across ten Asian reporter-country cohorts, including Pakistan, and test its relationship with the number of named medication entries.

Data:

Analysis of openFDA reports in calendar years 2021–2025 was reanalyzed independently in two tasks of this same study. The report was considered qualified if it contained the MedDRA term "drug interaction" or at least one role of a drug involved in the interaction. The primary endpoint was at least three interacting-role entries among reports listing at least three drugs. Report-level robust logistic regression was used to estimate country-specific Wilson intervals and to adjust associations; different inclusion and outcome rules were employed.

Results

Among 884 archived interaction-related reports from 10 countries, 646 included three or more named drugs and 268 fulfilled the multi-role endpoint. Pakistan contributed 38 eligible reports, of which 12 met the endpoint. In the six-country adjusted analytic set (n = 629), each doubling in named-drug count was associated with greater odds of multi-role coding (OR 2.11, 95% CI 1.65–2.68); sensitivity estimates were directionally consistent.

Conclusion

Multi-role attribution is common in this selected pharmacovigilance extract and varies by reporting context. Because the outcome is partly constrained by medication-entry count, the findings concern report coding and cannot establish a true drug–drug interaction, incidence, causality, or pharmacological mechanism.

1 Introduction

Preventable medication-related harm remains a central concern for clinical pharmacy, particularly in settings where multiple agents are used simultaneously. Polypharmacy and medication-review processes are mentioned by WHO as important targets to achieve harm reduction (WHO 2019). Co-listing multiple drugs on a safety report does NOT indicate that the drugs were used simultaneously. It does not necessarily indicate a known mechanistic drug pair, nor an inherently preventable drug–drug interaction (DDI). DDI detection studies need to differentiate between drug exposure, suspected attribution, clinical adjudication, and regulatory report coding (Thakrar et al. 2007; Strandell et al. 2013).

Successful implementation of spontaneous reporting relies on the process to provide an important source of hypotheses for medication safety without giving a population-based risk cohort, however. It is well established that there is under-reporting and variation in individuals submitting reports (Hazell and Shakir 2006; Worakunphanich et al. 2022). An important recent systematic review in the target journal has also highlighted the lack of completeness and the contextual nature of formal Pharmacovigilance reporting (Nohr et al. 2026). Therefore, no interpretation should be made about differences in actual clinical DDIs, based on country-to-country differences in report composition.

Established pharmacovigilance studies have described suspected interaction reports in France and Italy (Leone et al. 2010; Létinier et al. 2021; Magro et al. 2021). Another, more recent EudraVigilance study examined psychiatric–somatic combinations and psychiatric drug combinations (Dubrall et al. 2025; Dubrall et al. 2026). Several international analyses of the distribution and typical medicines reported in broad FAERS DDIs have been provided (Alahmari et al. 2025). These studies highlight that the "discovery" of "interacting drugs" by geographic stratification or by changing the name of a standard metric is not enough and in itself does not mean "discovery" and/or "publication" priority.

The clinical-pharmacy question explored here is narrower. The structured regulatory interacting-drug role may be associated with more than one entry for a drug. If multiple such assignments are indicated on a report, then perhaps further expense across pharmacist-led items is warranted, as this can be more complex to interpret than a one-role report. However, this is merely a documentation-complexity hypothesis: role-coded drugs are not bioscience-validated two-drug or higher-order interactions. Multiplicity is also mechanistically connected to the number of drugs recorded at the report level, and any investigation is required to identify this and not interpret the coefficient as a consequence of some sort of interference between the drug and the system.

This is a geographical focus inspired by the importance of being safe with medicine in Pakistan and other South Asian countries. There have been concerns about QT-prolonging combinations of medicines as documented in hospital research in Pakistan (Khan et al. 2017), and pharmacovigilance guidance has been issued by the Drug Regulatory Authority of Pakistan (DRAP 2025). A multinational analysis of the approach to coding each of these categories can unveil patterns that make it possible to design cautions training or data-quality audit systems without mixing up how drugs are reported and whether the patient is harmed by the drug.

To cope with that, we did a secondary analysis of an already public and publicly derived restricted openFDA extract. The main question was: Is there an increase in recorded burden of medication associated with an increased likelihood of having at least 3 interacting-role entries, adjusted for reporter-country, report year, reporter qualification, and the independent MedDRA "Drug interaction" reaction term. This research question is not the same as the concordant endpoint of the accompanying uploaded paper, but due to the shared use of the underlying report subset, editorial evaluation for both regarding overlap and scientific incremental value is critical. It is not a new, independent analysis nor an unreported pharmacological mechanism.

2 Aim

This aimed to identify associations between recorded medication burden in 10 country cohorts of Asian origin and the distribution of the reports of three or more interacting drugs, where at least three drugs had been reported, across Pakistan as well as other nine country cohorts, and to characterize this distribution. We also tried to determine the magnitude of change in the adjusted reporting-outcome estimates with prespecified restrictions without assuming biological drug interactions and clinical event rates.

3 Method

3.1 Data source, provenance, and report cohort

This is a post hoc study that reevaluated the case-level projection provided in the first user-provided research package. The original source was the US Food and Drug Administration's openFDA interface to the publicly available FDA individual case safety reports (ICSRs), which are coded according to international pharmacovigilance standards (FDA 2024; FDA 2026a). The archived snapshot was labeled 28 October 2026, and its source query URLs accompany individual rows. The FDA has publicly released the API structure, definitions of which fields are searchable and available, and has a dashboard of information about the current report availability that is made public (FDA 2026c). The original data endpoint was not accessible during network operations, so a 're-download' was not undertaken as part of the current project, and this aspect is acknowledged throughout the project.

Ten countries, namely Pakistan (PK), India (IN), Bangladesh (BD), Sri Lanka (LK), Nepal (NP), Thailand (TH), Malaysia (MY), Philippines (PH), Indonesia (ID) and Singapore (SG), were randomly selected to represent different country codes. Receipts have been reported for the 2021–2025 period. The previous archive had occurred country, and a case-selection criterion of MedDRA reaction preferred term of 'Drug interaction' or the presence of at least one MedDRA drug characterization code of 3 (interacting-drug role). Even with limited extraction, filtering out any clinical narratives, drug identifiers, or patient demographic information has been avoided: these report identifiers had already been hashed. The author verified the uniqueness of the report hash, year bounds, and country membership, and that counts of interacting roles did not surpass named-drug report counts. In line with all secondary FAERS studies,

report selection and deduplication decisions affect the outcomes of this analysis (Banda et al. 2016; Kreimeyer et al. 2025).

3.2 Variables and primary estimand

The unit of analysis was the individual archived report record, not a patient or a prescription. This number of patient-drug objects in that report was called the drug-entry count. The number of such drug objects whose structured role was equal to 3 is called the interacting-role count. It does not measure suspected potential interacting pairs, pharmacokinetics interactions, or evidence that coadministration was done. For qualified records, at least three types of drugs in the record had names. The most important binary outcome was three or more "interacting-roles" entries on eligible reports. The probability of the estimand—the probability of a structured reporting outcome in the selected archive and not the probability of a true clinical adverse DDI. An alternative two-role outcome, a report-level role fraction (number of interacting-role entries/number of named drug entries), was suggested as secondary characterization.

3.3 Statistical analysis

Each country's total reports, number of people eligible for the three-drug threshold, number of incidents, and proportion with the primary outcome were summarized. The score intervals for each of the Wilson's are for uncertainty within the extract, not for selectivity of reporting or randomness in the national sample. The logistic analysis, to characterize in a covariate-adjusted manner, was limited to country cohorts with 20 or more archived reports, which were chosen prior to model fitting to avoid complete-separation problems. Those countries with lower reporting numbers were kept as descriptive tables and figures. The primary binary endpoint was the logistic response, and the predictors were the log2(named-drug count), physician qualification vs all other or missing qualifications, and the fixed country indicators (Pakistan reference) and categorical receipt year (2021 reference) and the explicit interaction reaction term. 95% Wald intervals were computed from the heteroskedasticity-consistent (HC1) report-level standard errors.

Collectively, country terms were evaluated with a nested comparison of the fits of the models, which was exploratory given the different composition of cases and reporting cultures and the purposive selection of the country panel. Also shown is a weighted fractional-logit description of interacting-role fraction with report-level robust uncertainty, which is not a binomial trial of independent patient exposures. The main regression coefficient for log2(named-drug count) is necessarily somewhat structural: it can't be three interacting-role assignments unless at least three drugs are included in the report; more assignments are possible with more entries. Explicitly, we will not interpret the coefficient as a biologically independent effect of the medication.

3.4 Prespecified robustness checks

We reran the principal model after excluding records with > 20 entries for drugs; limiting the time period to 2023–2025; changing the three-role outcome to ≥ 2 roles (any record with ≥ 2 drugs reported); and

only including records whose reporter-source country code was the country of occurrence. Results are expressed as association between sensitivity of reporting and code; this is not evidence of causal robustness. We did not use reporting odds ratio for drug-event disproportionality as the archived projection does not have complete strata for drug-specific exposure and background non-case events. Thus, the READUS-PV recommendation does not imply that the traditional disproportionality analysis was conducted (Fusaroli et al. 2024a; Fusaroli et al. 2024b; Noguchi et al. 2021).

3.5 Reporting, reproducibility and source limitations

The analytic data are provided as the original saved projection, with a dictionary that can be altered and all the code to get the country summaries, regression estimates, etc., with a clean Python environment. The analysis was verified with the limits of the receipt year and the uniqueness of hashed IDs, as well as the country membership and cohort size from the source package. To the extent they were applicable to a retrospective archive, the STROBE and RECORD-PE principles were followed (Langan et al. 2018; Nie et al. 2018). We do not have any laboratory measurements of the drug-specific in-house experimental data or any patient-specific treatment history data available. Therefore, this manuscript is an exploratory – coding – methodology study and not a study to determine therapeutic efficacy or mechanism.

4 Ethics approval

Pharmacovigilance extract, which was publicly derived, reduced, and archived, was only analyzed. Provided records include hashed versions of report identifiers and no patient information that could directly identify a patient. There was no new contact, intervention, or institutional human subjects study conducted. No external ethics approval is ascribed, and it is up to the responsible author's institution to determine whether a formal exemption or ethics approval is required.

5 Results

There were 884 individual records of reports in the archived cohort from 2021–2025, across 10 countries. All records met the selection criteria of an explicit interaction preferred term or one sensitivity to interacting drug characterizations at least. Primary three-medication thresholds accounted for 73.1% (646) of the reports; of which, 41.5% (268) had at least three interacting-role reports. The analytic populations are described in detail in Table 1. As shown in Fig. 1, this is not a new-download PRISMA flow diagram, but instead the non-independent eligibility and endpoint steps.

Table 1
Cohort definition, data provenance and analytic denominators.

Item	Value
Source study period	2021–2025
Selected occurrence countries	10: PK, IN, BD, LK, NP, TH, MY, PH, ID, SG
Archived individual reports	884
Reports with at least 3 named drugs	646
Reports with ≥ 3 interacting-role entries	268
Countries in six-country adjusted model	IN, TH, MY, PK, ID, SG
Adjusted model eligible reports	629
Data provenance	Archived reduced openFDA source extract; no new API pull

Between-country differences in the proportion with at least three interacting-role assignments were appreciable, but several cohorts were very small. Table 2 reports all ten country counts, Wilson intervals, median medication entries, and overall role fractions. The descriptive points and intervals are shown in Fig. 2. In Pakistan, 12 of 38 eligible reports (31.6%) met the endpoint. Interpretations of national population risk are unwarranted because sampling, reporting eligibility, and drug exposure denominators are unknown.

Table 2
Country-wise high-multiplicity interacting-role coding and within-extract Wilson confidence intervals.

Country	All n	Eligible n	Events n	Event % (95% CI)	Role fraction %
IN	608	419	171	40.8 (36.2–45.6)	39.8
TH	81	72	27	37.5 (27.2–49.0)	32.8
MY	54	46	14	30.4 (19.1–44.8)	33.6
PK	44	38	12	31.6 (19.1–47.5)	44.8
ID	39	32	24	75.0 (57.9–86.7)	55.9
SG	27	22	8	36.4 (19.7–57.0)	38.7
NP	15	9	6	66.7 (35.4–87.9)	32.1
PH	8	5	3	60.0 (23.1–88.2)	65.6
LK	6	1	1	100.0 (20.7–100.0)	50.0
BD	2	2	2	100.0 (34.2–100.0)	50.0

For the adjusted analysis, six countries met the prespecified ≥ 20 archived-report criterion and supplied 629 eligible reports (256 endpoint reports). The adjusted association per doubling of named drug entries was 2.11 (95% CI 1.65–2.68), with a two-sided p-value of 1.7e-09. A collective exploratory test for country covariates gave χ^2=23.81, five degrees of freedom (p = 0.0002357); this test does not establish national treatment differences. Table 3 displays the explanatory estimates, and Fig. 3 shows selected estimates against the null.

Table 3
Robust multivariable logistic model for ≥ 3 interacting-role entries among reports listing ≥ 3 drugs (six-country analysis).

Predictor	Adj. OR	95% CI	p-value
Named drug entries (each doubling)	2.11	1.65–2.68	1.732e-09
Physician reporter vs other/unknown	1.46	1.00–2.15	0.05007
Explicit interaction reaction term	0.46	0.27–0.80	0.005661
Indonesia vs Pakistan	13.93	4.47–43.35	5.46e-06
India vs Pakistan	2.91	1.43–5.92	0.003086
Malaysia vs Pakistan	2.25	0.83–6.05	0.1093
Singapore vs Pakistan	3.22	1.08–9.59	0.03557
Thailand vs Pakistan	2.34	1.04–5.28	0.04067

Alternative eligibility windows and outcome definitions yielded positive, but not causally interpretable, associations for drug count. The point estimates for each sensitivity model and their heteroskedasticity-robust intervals are provided in Table 4 and Fig. 4. The drug-entry model cannot adjust for therapeutic indication, comorbidity, medication administration, polypharmacy appropriateness, pharmacogenomics, or a confirmed drug-pair mechanism, since none was retained in the source archive.

Table 4
Sensitivity scenarios for the adjusted association between named-drug count and multi-role coding.

Specification	Reports	Events	OR	95% CI
Primary ≥ 3 roles / ≥3 drug entries	629	256	2.11	1.65–2.68
Exclude > 20 drug entries	611	239	1.93	1.48–2.52
Years 2023–2025 only	326	148	1.78	1.34–2.37
≥ 2 roles / ≥2 drug entries	830	489	1.92	1.58–2.32
Reporter and occurrence country concordant	619	253	2.13	1.67–2.72

6 Discussion

This multi-country analysis reported a relatively high number of spontaneous reports of three or more interacting-drug role assignments in a chosen archive that contained reports of these types for Pakistan. It is operationally relevant for drug use safety documentation, as a clinical pharmacist faced with such documentation would have to address the actual method of administration, dosage, time, drug combination partner, and clinical outcome on a case-by-case basis. It doesn't indicate whether or not high-order interaction is prevalent in patients. The regulatory role is not a pharmacologically validated event, but a reported event in the report.

The strong, direct relationship between the number of drug entries and the multi-role endpoint is not to be interpreted as independent causal evidence; this outcome definition very much depends on the fact that at least 3 entries for a given drug appear and the number of drug entries imposes the maximum number of interacting-role assignments for a given patient. Even if only records containing at least three drugs are considered, this dependency will still remain between the two drugs, as no one will be present in that instance. Even a large adjusted odds ratio may therefore arise from the mechanics of coding without any increase in true interaction severity. This is the reason why caution and description are a better interpretation of role-multiplicity than the clinical risk is the outcome of the study. Similar construct-validity issues also play a key role in pharmacovigilance signal methods (Strandell et al. 2013, Noguchi et al. 2021).

Geographic variability is probably influenced by a combination of reporting routes, level of maturation of the pharmacovigilance system, as well as report authorship, availability of the drug and indications, and the extent of coverage of the systems. There were not many archived reports in Pakistan; only three other South Asian countries had fewer than 20. Thus, apparent precision of the pooled model, or an exploratory country test, does not solve representativeness. These percentages should not be regarded as national incidence rates for direct medication reconciliation, and completeness of original reports should be targeted in local clinical pharmacy and pharmacovigilance capacity initiatives (DRAP 2025, Worakunphanich et al. 2022 and Nohr et al. 2026).

The study builds on but has to deviate from previous observational studies of interaction. An interaction was reported at the case level, in Italy (Leone et al. 2010) and France (Létinier et al. 2021; Magro et al. 2021), with varying levels of ability to detect drug combinations. Recent psychiatric EudraVigilance investigations also indicated that drug identities and clinical context are of significance (Dubrall et al., 2025; Dubrall et al., 2026). Alahmari et al. (2025) already performed analysis in a large FAERS DDI-report population, and there isn't really much novelty on the part of using FAERS, the broad geography, or the descriptive nature of the interactions. There is some overlap in materials in the present archive, which was originally employed in a separate term-versus-role concordance study. This analysis must therefore be shown openly as a derivative exploratory study and not as independent validation, or a discrete pharmacological discovery.

External validation would require a genuinely independent dataset preserving drug identities, administered doses, treatment periods, laboratory markers, and adjudicated clinical outcomes, ideally with active comparators and complete background reporting. This can include enzyme inhibition or induction, or transporter effects, while pharmacodynamic combinations can result in additive toxicity without any alteration in drug concentrations. All of these mechanisms were not tested here. In general, readers of journals should consider the current endpoint as a surveillance endpoint rather than an example of drug action if the dose-exposure-response relationship and the interaction between the drug event and the endpoint were not explicitly measured. Defining and estimating a synergy score for a clinically meaningful interaction is also not possible due to a lack of an available drug-pair field.

Recent studies in the target journal show that pharmacovigilance analysis is in scope when it yields genuinely informative, well-defined pharmacological safety hypotheses. Persistent representation of FAERS data in quarterly graphics highlights the need to investigate trends over time (temporal) stability, and $\chi 2$ stratification of antiarrhythmic reporting by sex underscores the need for meaningful clinical stratification. The current limited extract does not allow for a comparable signal persistence for each drug; neither can it make a 'mechanism-aware' contrast. It is its narrowness that makes it a probable source of desk rejection, and this will not be solved by stylistic changes or more citations.

More broadly, international pharmacovigilance methods now emphasize transparent provenance, precise coding, recognition of duplicates, and reporting of all filtering choices. The drug-event metadata in the openFDA are updated from time to time and do not represent a stable population cohort (FDA 2026a, FDA 2026b, FDA 2026c). MedDRA also warns about the use of an administrative preferred term as a clinical adjudication (MedDRA MSSO 2026). The material impact of terminological harmonization and handling the duplication is evident in published standardization efforts (Banda et al. 2016; Kreimeyer et al. 2025). This means that the exact source projection that was reduced, original query URLs per record, and deterministic analytic code are included in the package.

There are a number of limitations in this research. First, there are publication-overlap and selection-bias issues because the report's latest projection was based on the previous projection, and a second independent report was not obtained. Second, figures for each country are not equal and frequently very small. Third, it is a binary outcome of high multiplicity that is not verified by exposure and is mechanically dependent on the number of entries in the drug group. Fourth, there is no information needed on age, sex, comorbidity, actual administration, drug identity, DDI classification, and clinically adjudicated severity. Fifth, report corrections or duplicate records beyond the saved hashed-ID projection cannot be checked independently. Ninth, spontaneous reporting fails to provide national denominators, nor will it indicate causality of pharmacological effects. Finally, the original analysis being AI-assisted and based on public data cannot truthfully satisfy the target journal's required in-house/no-AI author attestation.

The bottom line for clinical pharmacy administrators is one of data-audit priority – complex interaction-related safety reports could be triaged for drug-pair reconciliation, complete medication histories, and

standardized role assignment. A future prospective study should evaluate its effectiveness as an intervention in adjudication accuracy and/or in minimizing medication harms. The following next-step hypothesis was not explored clinically here. Recommendations for quality improvement, therefore, should be distinguished clearly from evidence of effectiveness of an intervention.

7 Conclusion

In a historical series of interaction-related pharmacovigilance reports submitted from Pakistan and nine comparator countries, more than one drug was involved in the interaction, and the number of assigned drugs was higher for multiple interacting-drug role assignments than for other drug assignment roles. These are exploratory documentation data and are NOT national incidence numbers, confirmed clinical DDIs, or pharmacologic data. Due to the overlap of the source records with an earlier published paper, as well as the journal attestation requirements conflicting with the current workflow, this work should be left as a research draft until the information can be collected independently and submitted to an editorial policy review and human validation.

Declarations

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Competing interests

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Author contributions and generative AI

Sameer Farooq contributed to the critical evaluation of the study design, validation of the analytical procedures and interpretation of findings, and substantive revision of the manuscript. The final manuscript has been reviewed and approved for submission by the author. All analyses of the data presented here and subsequent research products were performed in-house from secondary data sources openly available on the internet. The author also states that no paper mill or commercial manuscript preparation service was used in any part of the research and writing process. The original science or scientific findings, analyses, or figures were not created using generative artificial intelligence. This does not mean it was used to directly influence the content of the manuscript. Without exception, it was used only for proofreading language, and it was also separately disclosed.

Ethics approval and consent

The analysis used previously collected, public, reduced pharmacovigilance records and involved no intervention or contact with individuals. A formal local ethics determination has not been documented.

Consent was not obtained by this secondary-analysis workflow; the FDA source is a publicly released pharmacovigilance archive.

Data availability

An analysis-ready derived set of CSVs, analysis results as a JSON archive, and the complete Python code are provided in the attached zip. The reduced projection includes the original openFDA query source URLs and snapshot dates. This package does not contain new original FAERS downloads or named drug-pair data.

Code availability

Reproducible code for all numerical results, country summaries, regression fits, and figures is supplied in scripts/analyze.py.

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Figures

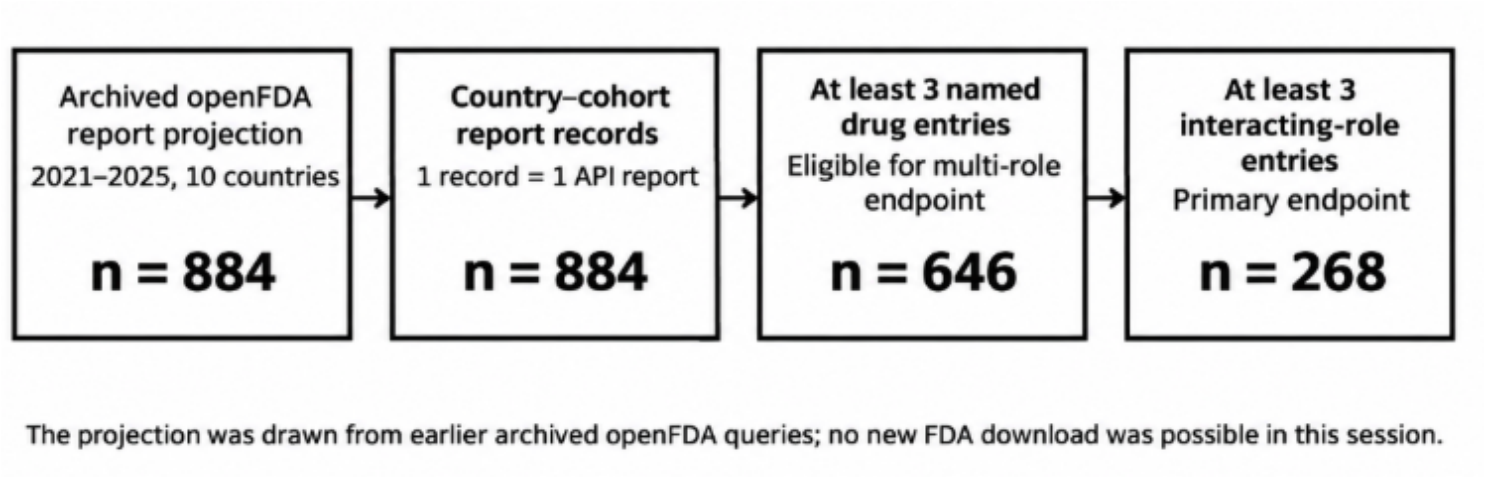


Figure 1

Report selection and primary-endpoint definition. Counts are report records; the archived source extract originated from previously collected openFDA queries.

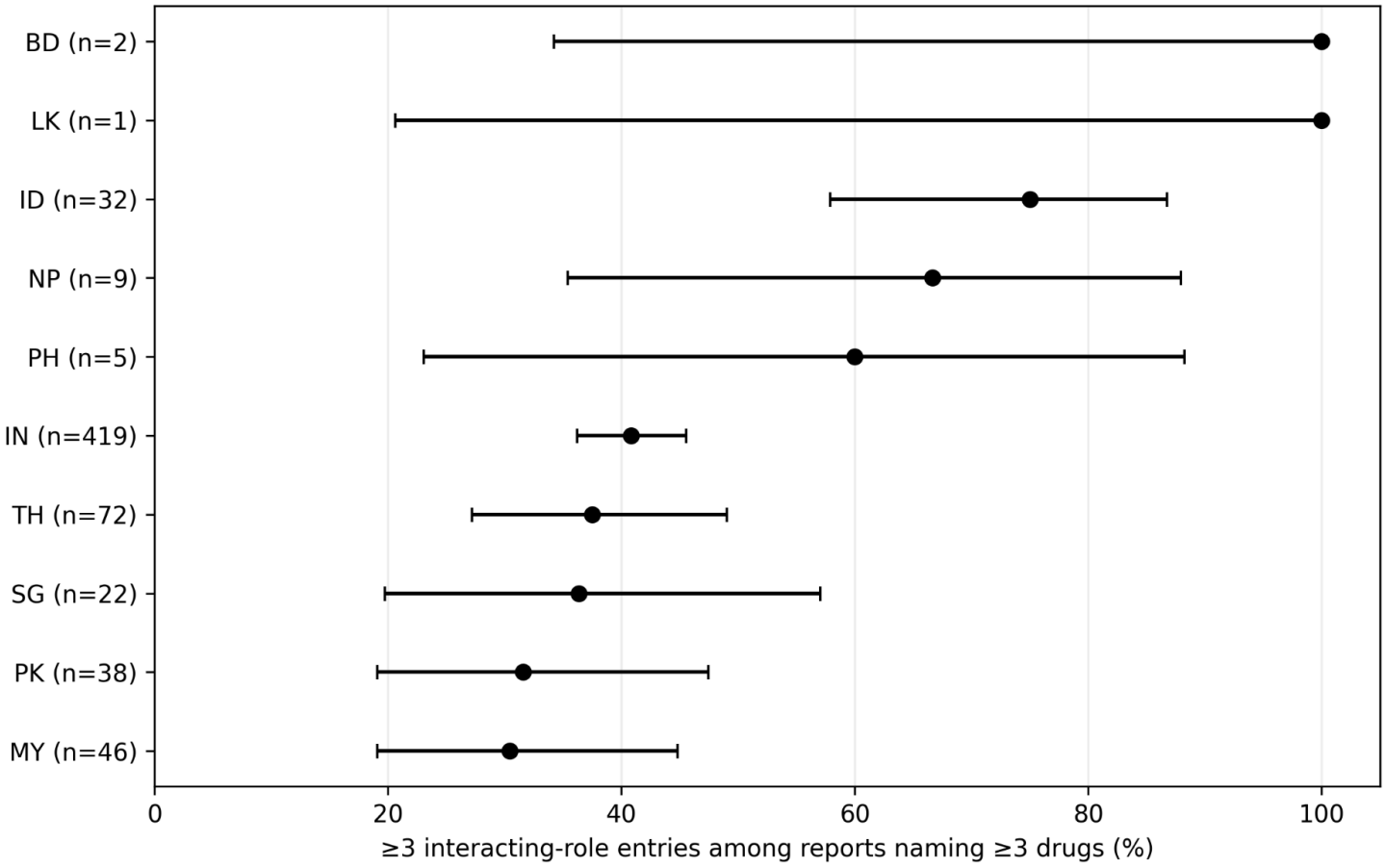


Figure 2

High-multiplicity role-coding proportions by country, with report-level 95% Wilson intervals. Rare country cohorts must not be over-interpreted.

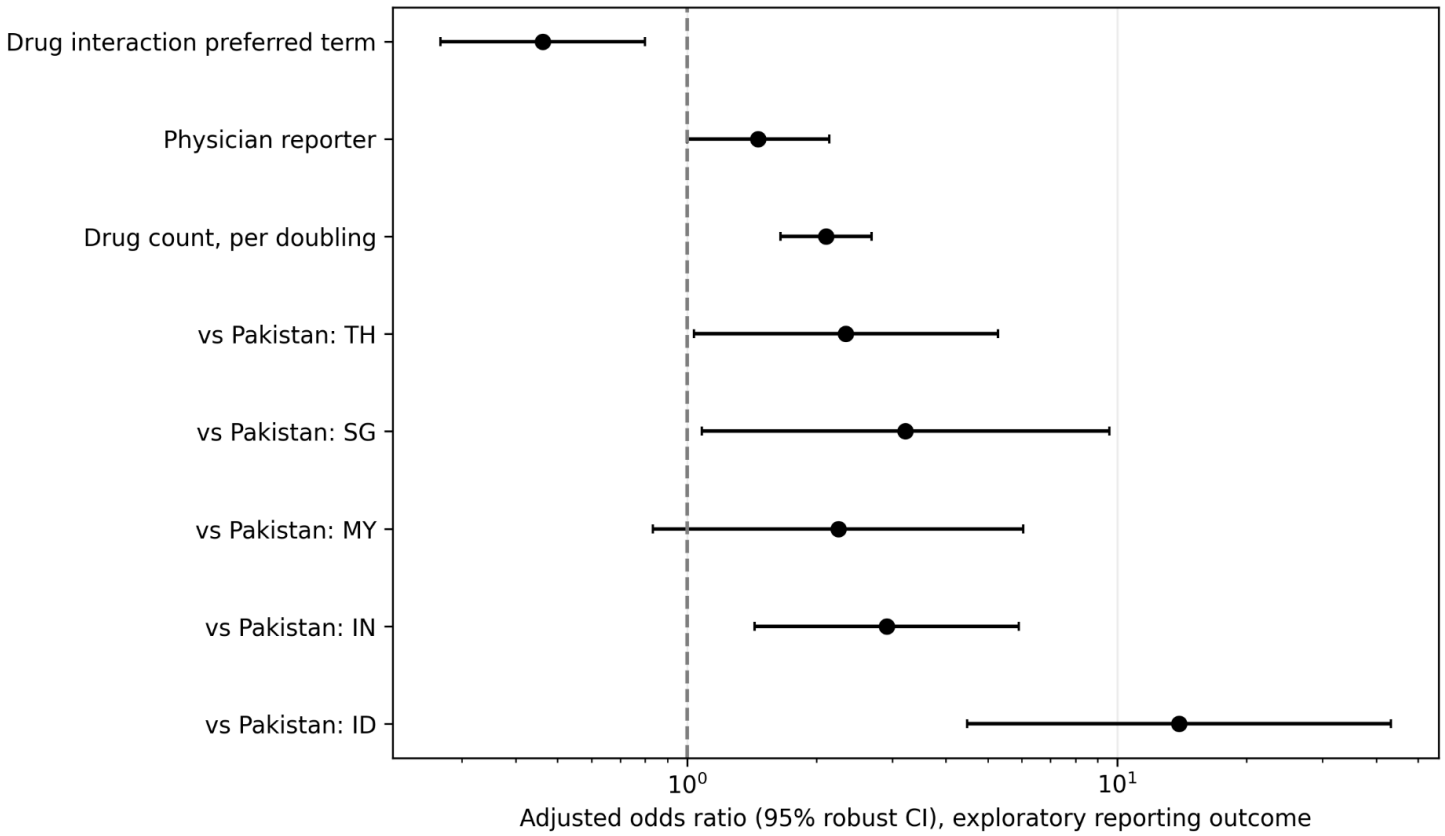


Figure 3

Exploratory adjusted reporting-outcome associations. The drug-count predictor has an intrinsic mathematical relation with the three-role endpoint.

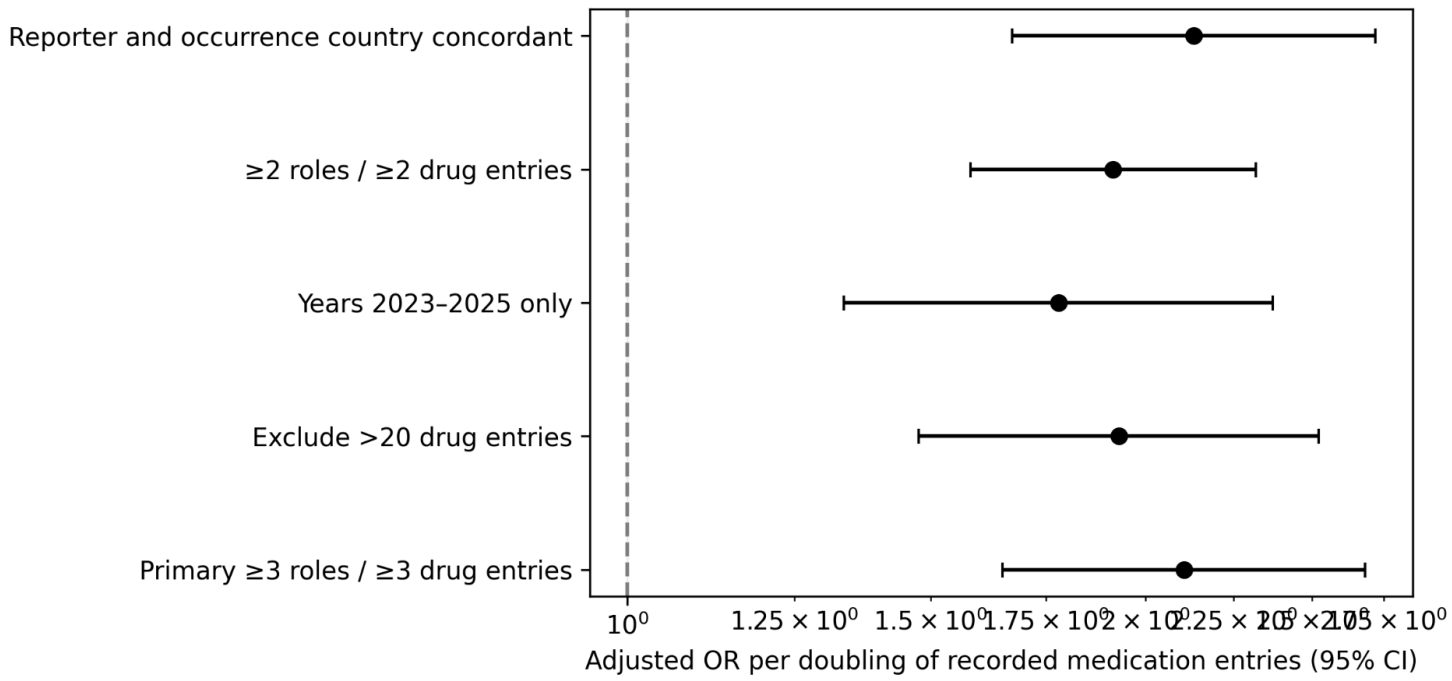


Figure 4

Sensitivity of the recorded drug-count association to eligibility, time period, coding threshold and country-concordance restrictions.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- primaryregression.csv
- results.json
- attachedpapersourcecomparison.csv
- drugbandsummary.csv
- archivedopenFDAinteractioncaseprojection.csv
- yearsummary.csv
- countryanalysis.csv
- rolefractionregression.csv
- sensitivity.csv
- analyze.py