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RESEARCH ARTICLE
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BETWEEN-CENTRE VARIATION IN THE PROPORTIONS OF ADVERSE DRUG REACTIONS GRADED BY CAUSALITY, SEVERITY AND PREVENTABILITY IN INDIAN TERTIARY CARE CENTRES

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Abstract

Background. Most Indian ADR monitoring centres (AMCs) publish audits that grade reports with the WHO-UMC causality system, the Hartwig-Siegel severity scale and the modified Schumock-Thornton preventability criteria. Their headline proportions differ widely and have not been synthesised.

Methods. This is a pilot analysis of a convenience sample, run before a logged systematic search; all criteria were set after the included papers had been read. Observational studies from Indian tertiary care hospitals that graded ADRs from all drug classes with WHO-UMC causality were eligible. Raw counts were extracted by one reviewer. Proportions were pooled on the logit scale with DerSimonian-Laird τ^2 and Hartung-Knapp-Sidik-Jonkman (HKSJ) confidence intervals; REML, Paule-Mandel and a binomial-normal GLMM were sensitivity analyses. Preventability was summarised descriptively.

Results. Eleven of 21 unique reports were included, covering 2,001 reports. The share graded probable ranged from 22.5% to 91.4% between centres (I^2 96%, τ^2 0.77; prediction interval 23.3 to 95.1); the pooled value was 70.9% (54.1 to 83.4). Across eight studies grading severity, the severe share ranged from 1.8% to 18.4% (pooled 8.2% (4.2 to 15.4)). The six centres reporting preventability judged between 0% and 97% of reactions not preventable. The lowest probable share came from the only active surveillance study. There was no evidence that region, inpatient setting or year explained the causality variation, although with 11 studies these analyses had little power.

Conclusions. Published Indian AMC audits differ widely in how their reports are distributed across causality, severity and preventability grades, so no single pooled figure represents them. Because each centre graded different reports, this design cannot separate case mix from grading practice. A logged systematic search, a second reviewer and a multicentre regrading study are needed before firm conclusions.

Keywords: Adverse drug reactions; Pharmacovigilance; WHO-UMC causality assessment; ADR severity; Preventability; Indian Adverse Drug Reaction Monitoring Centres.

1. Introduction

Background and rationale

An adverse drug reaction is a noxious and unintended response to a medicine given at a normal dose.[1] Serious reactions affect about 6.7% of hospital inpatients[2] and account for about 6.5% of admissions.[3] The Pharmacovigilance Programme of India collects spontaneous reports through ADR monitoring centres, most of them in medical college pharmacology departments.[4] Under-reporting limits every spontaneous system.[5] Many centres have published audits of their own reports, and most use the same three instruments: the WHO-UMC causality system,[6] the Hartwig-Siegel severity scale[7] and the Schumock-Thornton preventability criteria in their three-category modified form.[8,9]

The headline figures from these audits differ widely. Some centres grade most reports possible and others probable; some judge nearly all reactions preventable and others almost none. Preventability estimates in general vary with the method used.[10] Two explanations are possible. Centres may receive different reactions, or they may apply the same scales differently. A synthesis of published audits can measure how large the variation is, but because each centre graded its own reports it cannot tell these explanations apart.

Objectives

To estimate the pooled proportions of ADR reports graded probable (primary), certain or probable, possible, mild, moderate and severe in Indian tertiary care audits; to describe the share judged not preventable; and to quantify between-centre variation and explore whether region, setting or period explain it.

2. Methods

The review follows PRISMA 2020.[11] This is a pilot analysis, and no protocol was registered before it. Every eligibility criterion, outcome and handling rule below was set after the included papers had been read.

2.1 Eligibility

Element	Criterion
Population	Patients of any age at Indian tertiary care hospitals with a suspected ADR reported to an AMC or found through hospital surveillance.
Condition	ADRs from any drug class graded with the WHO-UMC causality system, with a usable denominator.
Context	Spontaneous reports analysed by an AMC, or active inpatient surveillance; outpatients, inpatients or both.
Excluded	Series limited to one drug class or organ system; causality by the Naranjo algorithm only, which does not map onto WHO-UMC categories;[12] studies without grading data; reviews.

2.2 Outcomes

The primary outcome was the proportion graded probable. Secondary outcomes were certain or probable combined, possible, and mild (Hartwig-Siegel levels 1 to 2), moderate (3 to 4) and severe (5 to 7).

Probable alone was chosen as primary because the certain category also requires a definitive pharmacological or phenomenological event (rechallenge only if necessary), which spontaneous report forms rarely document. Certain or probable is reported as the first secondary outcome for comparison with published audits. Each category was pooled separately, so pooled severity grades are not constrained to sum to 100%. The proportion judged not preventable was summarised without pooling. The sex of patients was not analysed, because without the sex distribution of the exposed population it carries no information on susceptibility.

2.3 Information sources and selection bias

This pilot uses the full texts assembled by the authors: 24 files, 21 unique reports. Several came from the authors' own department and the rest from an unlogged web search. This is a convenience sample, not a systematic search, and selection bias is the main threat to every estimate below.

2.4 Extraction and handling rules

The unit of analysis was the graded case as each study reported it, which was the individual ADR in ten studies; Gupta 2025 graded per report and was removed in a sensitivity analysis. Six rules were applied and each was tested where possible.

Counts from percentages. Three studies printed percentages only.[13 to 15] Counts were back-calculated from the stated denominator and checked against category totals. For Jindal 2023, 41% of 148 gives 60.7; 61 was used and 60 tested. Two authors of this review are authors of Jindal 2023.

Reports and reactions. Gupta 2025 graded causality per report (200 reports, 282 reactions); 200 was used.[16]

Unaccounted reports. In Singh 2017 the causality categories sum to 231 of 232; the missing report was counted as neither probable nor possible.[17]

Abstract against tables. Where they disagreed, the table was used (Table 6).

Study at high risk of bias. Imran 2023 does not name its hospital or state its design, and its title describes outpatients although its data cover inpatients only.[18] It was kept in the primary analysis, rated high risk of bias, and removed in a sensitivity analysis.

Setting and reporting mode. Each study was coded once and the codes were used in every analysis. Reporting mode: spontaneous reports analysed by an AMC (nine studies) or active inpatient surveillance (Chandrabhan 2021 only). Setting: inpatients only (Imran 2023, Yadav 2025, Chandrabhan 2021) or mixed. Because the single active surveillance study is also inpatient-only, setting and reporting mode are partly confounded. Every study reporting preventability used the three-category modified Schumock-Thornton criteria (definitely, probably, not preventable).[9]

2.5 Risk of bias and certainty

Studies were appraised with the nine-item Joanna Briggs Institute checklist for prevalence data,[19] plus two items: whether the site was named and whether grading tables reconciled with the number of reports. Of the eleven items, a study meeting 8 or more was rated low risk of bias, 6 or 7 moderate, and 5 or fewer high. Certainty was rated with GRADE guidance for event rates.[20]

2.6 Statistical analysis

Proportions were logit-transformed with variance $1/x + 1/(n - x)$, adding 0.5 to both cells only for zero or complete counts. The primary model used DerSimonian-Laird τ^2[21] with HKSJ confidence intervals on $k - 1$ degrees of freedom,[22 to 24] with the scaling factor held at no less than 1; the floor never applied. Sensitivity analyses used REML and Paule-Mandel τ^2[25] and a binomial-normal GLMM fitted by maximum likelihood with profile-likelihood intervals, the approach recommended for single proportions with sparse or extreme counts.[26,27] The GLMM was fitted with custom code in Python 3.12 and SciPy 1.17, integrating the random effect numerically; its results are provisional until they are confirmed with meta::metaprop. Heterogeneity was summarised by I^2, τ^2 and Q,[28] with 95% prediction intervals.[29] Single-study intervals are Wilson intervals.[30]

Because I^2 exceeded 95% for most outcomes, the random-effects weights were nearly equal (8.5% to 15.5% per study), and pooled values lie close to an unweighted average on the logit scale. Ranges, τ^2 and prediction intervals are therefore reported first. Three exploratory analyses were run for each of six pooled outcomes: region (northern India, defined as Punjab, Haryana, Delhi, Uttarakhand, Himachal Pradesh, Jammu and Kashmir, Chandigarh, Uttar Pradesh and Rajasthan, against the rest; repeated with Rajasthan moved), setting (inpatients only against mixed), and random-effects meta-regression on the midpoint of data collection. That makes eighteen tests, so about one nominal p below 0.05 is expected by chance. Reporting mode could not be tested because only one study used active surveillance.

Analyses were written in Python 3.12 (NumPy, SciPy). The DerSimonian-Laird and HKSJ results were reproduced in statsmodels 0.15, which uses the same estimators and so checks the code rather than the method.

3. Results

3.1 Study selection and characteristics

Of 21 unique reports, three addressed other questions. Of 18 full texts, seven were excluded: four covered a single drug class or organ system, two used the Naranjo algorithm only and one reported no grading data (Figure 1; Appendix B). Eleven studies were included.[13 to 18, 31 to 35]

Stage	Records	Removed or pending
Identification	Full texts assembled: 24 Convenience sample; no logged database search	Duplicates removed: 3 Jindal 2023, Kumar 2023 and Dutta 2015 each present twice
Screening	Unique reports screened: 21	Excluded on title and abstract: 3 Medicine disposal KAP; package inserts; HIV quality of life
Eligibility	Full texts assessed: 18	Excluded at full text: 7 Single drug class or organ system 4; Naranjo only 2; no grading data 1

Stage	Records	Removed or pending
Included	Studies included: 11 2,001 ADR reports; one study at high risk of bias	Identified but not retrieved: 7 Await the systematic search

Figure 1. Study selection, PRISMA 2020 layout adapted to the assembled evidence base.

The eleven studies came from ten states and union territories, plus one unnamed site, and covered 2,001 reports collected between 2010 and 2024 (Table 1). Ten analysed spontaneous reports at an AMC; one used active inpatient surveillance. Three were confined to inpatients.

Table 1. Characteristics of eligible studies, ordered by period of data collection

Study	Site	Reporting mode	Setting	Period	Reports	Preventability scale
Dutta 2015[32]	Dehradun, Uttarakhand	Spontaneous, AMC	Mixed	Jan 2010 to Jun 2014	123	Not reported
Singh 2017[17]	Raipur, Chhattisgarh	Spontaneous, AMC	Mixed	Sep 2015 to Aug 2016	232	Not reported
Lhamo 2025[31]	New Delhi	Spontaneous, AMC	Mixed	Oct 2017 to Dec 2019	252	Modified, 3 categories
Chandrabhan 2021[35]	Jaipur, Rajasthan	Active surveillance	Inpatient only	6 months (dates not stated)	111	Not reported
Jindal 2023[13]	Faridkot, Punjab	Spontaneous, AMC	Mixed	Sep 2020 to Aug 2021	148	Modified, 3 categories
Imran 2023 ‡[18]	Not stated	Spontaneous, AMC	Inpatient only	Jan 2020 to Dec 2021	217	Not reported
Choudhury 2023[15]	Ranchi, Jharkhand	Spontaneous, AMC	Mixed	Sep 2020 to Aug 2021	161	Modified, 3 categories
Baby 2022[14]	Kollam, Kerala	Spontaneous, AMC	Mixed	Jan 2021 to Dec 2021	233	Modified, 3 categories
Gupta 2025[16]	Faridabad, Haryana	Spontaneous, AMC	Mixed	Jan 2022 to Dec 2022	200	Not reported

Study	Site	Reporting mode	Setting	Period	Reports	Preventability scale
Ram 2026[33]	Puducherry	Spontaneous, AMC	Mixed	Jan 2020 to Dec 2024	139	Modified, 3 categories
Yadav 2025[34]	Bambolim, Goa	Spontaneous, AMC	Inpatient only	Apr 2022 to Mar 2023	185	Modified, 3 categories

‡ High risk of bias (rule 5). Chandrabhan 2021 gives no dates; a 2020 midpoint was assumed for meta-regression.

Table 2. Data entered into the analyses (events/reports)

Study	Probable	Certain or probable	Possible	Mild	Moderate	Severe	Not preventable
Dutta 2015	91/123	93/123	30/123	NR	NR	NR	NR
Singh 2017	156/232	167/232	64/232	NR	NR	NR	NR
Lhamo 2025	202/252	230/252	22/252	150/252	78/252	24/252	174/252
Chandrabhan 2021	25/111	28/111	83/111	92/111	17/111	2/111	NR
Jindal 2023	61/148†	62/148†	84/148†	22/148†	123/148†	3/148†	0/148†
Imran 2023	186/217	191/217	26/217	66/217	111/217	40/217	NR
Choudhury 2023	97/161†	105/161†	56/161†	62/161†	74/161†	25/161†	34/161†
Baby 2022	137/233	139/233	90/233	29/233†	178/233†	26/233†	62/233
Gupta 2025	182/200	182/200	16/200	NR	NR	NR	NR
Ram 2026	127/139	129/139	10/139	9/139	124/139	6/139	135/139

Study	Probable	Certain or probable	Possible	Mild	Moderate	Severe	Not preventable
Yadav 2025	139/185	155/185	27/185	29/185	143/185	13/185	130/185
Total	1,403/2,001	1,481/2,001	508/2,001	459/1,446	848/1,446	139/1,446	535/1118

† Back-calculated from published percentages. NR, not reported. Not preventable is shown for completeness and was not pooled.

3.2 Causality

The share graded probable ranged from 22.5% to 91.4% (Figure 2). Heterogeneity was extreme (I^2 96.1%, τ^2 0.772), and the prediction interval ran from 23.3% to 95.1%, so the probable share at a new centre could lie anywhere from about a quarter to nearly all of its reports. The pooled value was 70.9% (54.1 to 83.4). Certain or probable together made up 75.5% (58.4 to 87.1), and possible 23.8% (12.4 to 40.8).

The lowest value, 22.5%, came from Chandrabhan 2021, the only active surveillance study, which was also inpatient-only.[35] Without it the pooled value was 74.9% (61.6 to 84.7); leave-one-out estimates otherwise stayed between 67.9% and 74.9% (Figure 6). The two spontaneous-report studies confined to inpatients graded 75.1% and 85.7% probable.[18, 34] There was no evidence that region (69.5% north against 71.9% elsewhere, p = 0.84), inpatient setting (63.6% against 73.2%, p = 0.61) or year (p = 0.69) explained the spread; with eleven studies these tests had little power (Table S1).

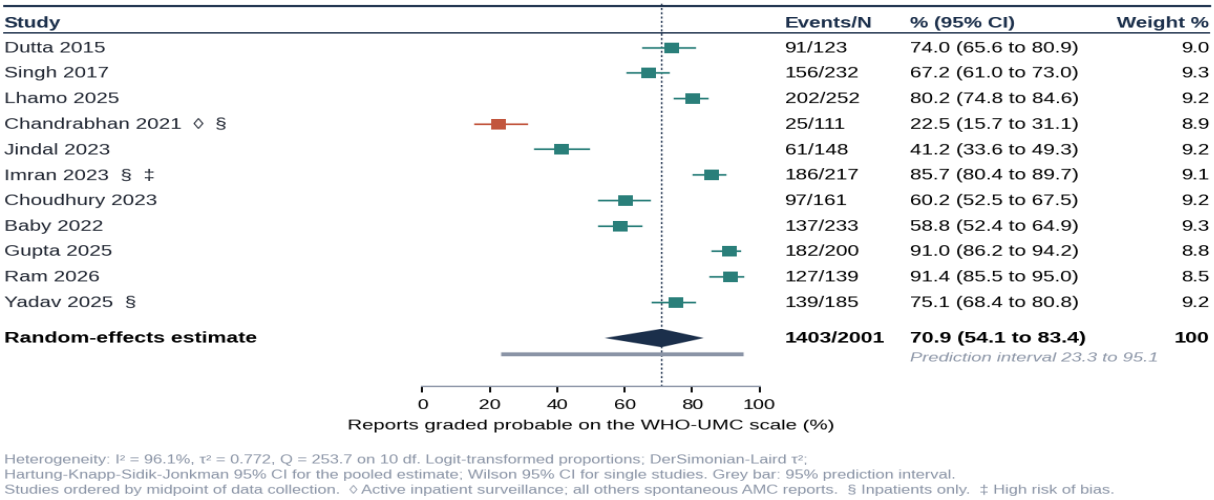


Figure 2. Reports graded probable on the WHO-UMC scale.

3.3 Severity

Eight studies graded severity. The severe share ranged from 1.8% to 18.4% and the mild share from 6.5% to 82.9%. Pooled, mild reactions made up 28.7% (11.2 to 56.1), moderate 60.6% (34.2 to 82.0) and severe 8.2% (4.2 to 15.4). Because each grade was pooled separately, the three estimates sum to 97.5% rather than 100% (Figure 3). For severe reactions I^2 was 83% and the prediction interval 1.9 to 29.5% (Figure 4).

In exploratory meta-regression, later studies graded fewer reactions mild (p = 0.020) and more moderate (p = 0.023). Because mild and moderate are close to complementary, these are one finding rather than two. It rests on eight studies, one with an assumed date, and no single study removes it: without Chandrabhan 2021 the slope for mild was −0.68 per year on the logit scale (p = 0.020), and without Lhamo 2025, the earliest study, −1.19 (p = 0.030). Northern centres also graded more reactions mild (p = 0.043). These are two of eighteen exploratory tests and should not be interpreted.

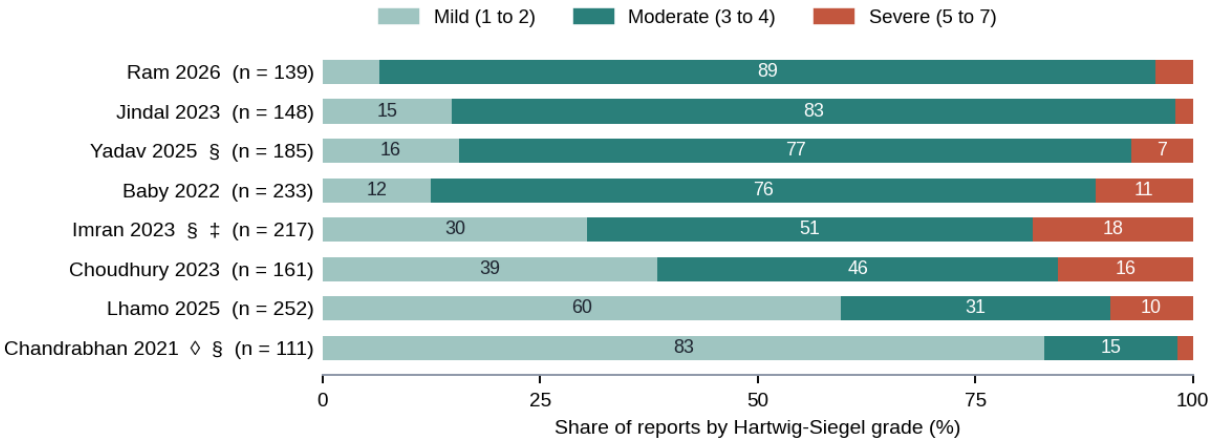
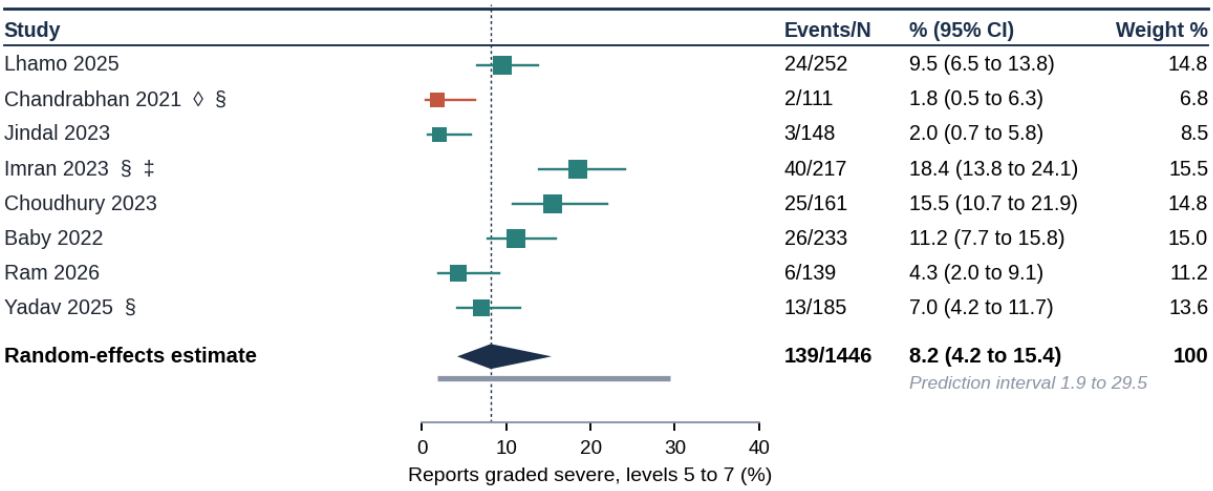


Figure 3. Severity profile of each study, ordered by the share graded moderate. Labels below 7% are omitted.

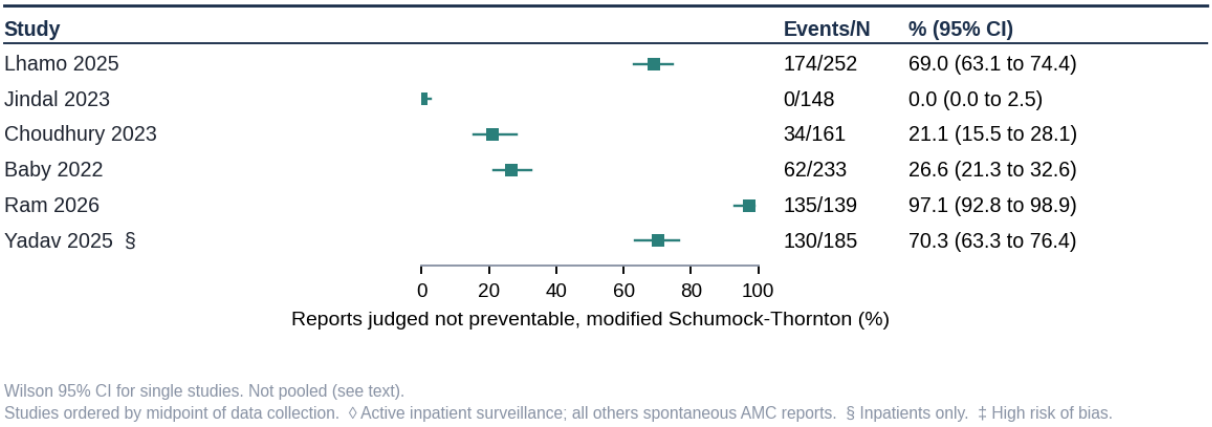


Heterogeneity: I^2 = 82.9%, τ^2 = 0.343, Q = 40.9 on 7 df. Logit-transformed proportions; DerSimonian-Laird τ^2;
Hartung-Knapp-Sidik-Jonkman 95% CI for the pooled estimate; Wilson 95% CI for single studies. Grey bar: 95% prediction interval.
Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure 4. Reports graded severe (Hartwig-Siegel levels 5 to 7).

3.4 Preventability

Six studies reported preventability, all with the three-category modified criteria. The share judged not preventable was 0%, 21%, 27%, 69%, 70% and 97% (Figure 5). These values were not pooled. Jindal 2023 recorded all 148 reactions as preventable, including 20 contrast and 20 vaccine reactions.[13] Ram 2026 judged 135 of 139 not preventable.[33] The scale version was the same in all six, so version differences do not explain the spread.



Wilson 95% CI for single studies. Not pooled (see text).
Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure 5. Reports judged not preventable, by study. Descriptive; not pooled.

3.5 Sensitivity analyses and alternative models

The choice of τ^2 estimator changed no estimate by more than 0.6 points, and the provisional GLMM agreed with the primary model to within 1 point for every outcome (Table 3). Removing Imran 2023 lowered the probable share to 69.0% and the severe share to 7.1%. Removing Gupta 2025, the one study graded per report, gave 67.9%. Entering Jindal 2023 as 60 rather than 61 probable changed the estimate by 0.1 points.

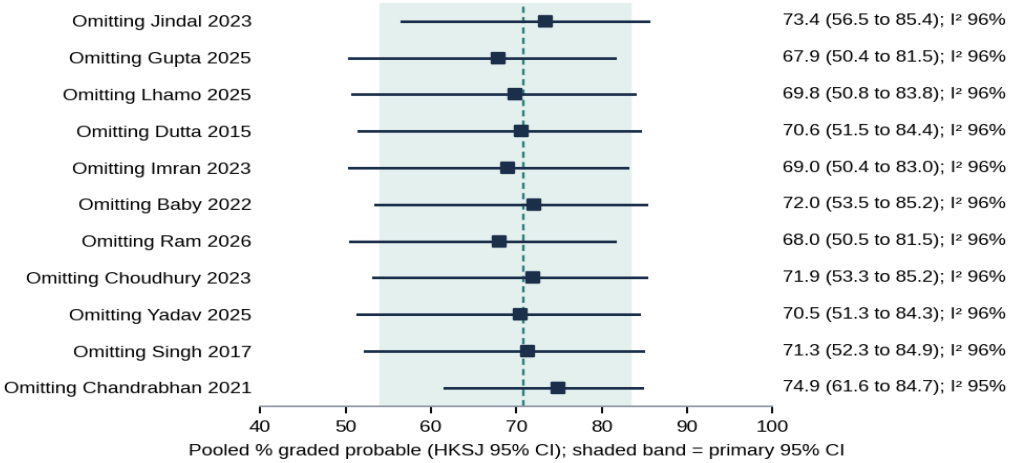


Figure 6. Leave-one-out analysis for the primary outcome.

Table 3. Primary model against alternative estimators, and sensitivity analyses

Outcome	DL + HKSJ (primary)	REML + HKSJ	Paule-Mandel + HKSJ	GLMM, profile CI (provisional)
Probable causality	70.9% (54.1 to 83.4)	71.0% (54.1 to 83.5)	71.0% (54.1 to 83.5)	71.1% (55.7 to 82.9)
Certain or probable	75.5% (58.4 to 87.1)	75.6% (58.5 to 87.2)	75.6% (58.5 to 87.2)	75.8% (60.2 to 86.7)
Possible causality	23.8% (12.4 to 40.8)	23.8% (12.4 to 40.8)	23.8% (12.4 to 40.8)	23.6% (12.9 to 39.0)

Outcome	DL + HKSJ (primary)	REML + HKSJ	Paule-Mandel + HKSJ	GLMM, profile CI (provisional)
Mild severity	28.7% (11.2 to 56.1)	28.6% (11.2 to 56.0)	28.6% (11.2 to 56.0)	28.4% (12.4 to 52.5)
Moderate severity	60.6% (34.2 to 82.0)	60.6% (34.2 to 82.1)	60.6% (34.2 to 82.1)	60.7% (37.2 to 80.2)
Severe	8.2% (4.2 to 15.4)	7.7% (3.9 to 14.9)	7.6% (3.8 to 14.8)	7.3% (3.7 to 12.7)

Sensitivity analysis	k	Estimate (95% CI)	I^2
Probable, excluding Imran 2023 (high risk of bias)	10	69.0% (50.4 to 83.0)	96%
Probable, excluding Chandrabhan 2021 (active surveillance)	10	74.9% (61.6 to 84.7)	95%
Probable, excluding the three inpatient-only studies	8	73.2% (55.4 to 85.8)	95%
Probable, excluding Gupta 2025 (graded per report, not per ADR)	10	67.9% (50.4 to 81.5)	96%
Probable, Jindal 2023 entered as 60 of 148	11	70.8% (53.9 to 83.4)	96%
Severe, excluding Imran 2023	7	7.1% (3.5 to 13.8)	77%
Moderate, excluding Chandrabhan 2021	7	67.4% (43.8 to 84.6)	97%

3.6 Summary of findings

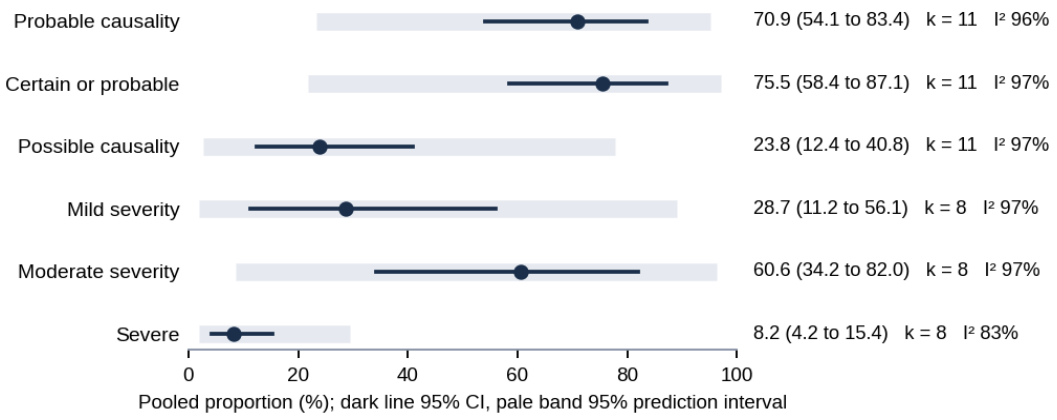


Figure 7. Pooled proportions. Dark line, 95% CI (HKSJ); pale band, 95% prediction interval. Severity grades were pooled separately.

Table 4. Summary of findings and certainty of evidence (GRADE for event rates)

Outcome	Studies (reports)	Pooled % (95% CI)	I^2	Certainty	Reasons for rating down
Probable causality	11 (2,001)	70.9% (54.1 to 83.4)	96%	Very low	Very serious risk of bias (convenience sample; spontaneous reports; three studies back-calculated); serious inconsistency (range 22.5 to 91.4%).
Certain or probable	11 (2,001)	75.5% (58.4 to 87.1)	97%	Very low	As for probable.
Mild severity	8 (1,446)	28.7% (11.2 to 56.1)	97%	Very low	Very serious risk of bias; serious inconsistency (6.5 to 82.9%).
Moderate severity	8 (1,446)	60.6% (34.2 to 82.0)	97%	Very low	Very serious risk of bias; serious inconsistency (15.3 to 89.2%).
Severe	8 (1,446)	8.2% (4.2 to 15.4)	83%	Very low	Very serious risk of bias; serious inconsistency (1.8 to 18.4%; prediction interval 1.9 to 29.5%).
Not preventable	6 (1,118)	Not pooled; 0 to 97%	NA	Not rated	Descriptive only.

Very low: the true proportion is likely to be substantially different from the estimate. Publication bias was not rated separately, because funnel methods are not interpretable for single proportions; the convenience sample is counted under risk of bias.

3.7 Risk of bias

Three studies were at low risk of bias, seven at moderate risk and one at high risk (Table 5). Appraisal was by a single reviewer.

Table 5. Risk of bias (JBI prevalence checklist, nine items plus two added items; low 8 or more, moderate 6 to 7, high 5 or fewer)

Study	Score	Judgement	Main concerns
Lhamo 2025	8/11	Low	Site named; all three scales reconcile
Ram 2026	8/11	Low	Five years of AMC records; counts reconcile
Yadav 2025	8/11	Low	Counts reconcile
Gupta 2025	7/11	Moderate	Causality only; abstract and methods give different totals
Baby 2022	7/11	Moderate	Severity printed as percentages only
Singh 2017	7/11	Moderate	One report unaccounted; no Hartwig-Siegel grading
Jindal 2023	6/11	Moderate	Causality as rounded percentages; preventability grading implausible; COVID period

Study	Score	Judgement	Main concerns
Dutta 2015	6/11	Moderate	No Hartwig-Siegel grading; data from 2010 to 2014
Choudhury 2023	6/11	Moderate	All results printed as percentages
Chandrabhan 2021	6/11	Moderate	Six months, dates not stated; three departments
Imran 2023	4/11	High	Site and design not stated; title describes outpatients but data are inpatients only

3.8 Reporting errors and inconsistencies

Ten errors or concerns were found in eight reports (Table 6). The most consequential are the unnamed site and inconsistent description of Imran 2023, and the preventability values of Jindal 2023.

Table 6. Reporting errors and inconsistencies

Report	Error or inconsistency	Handling
Jindal 2023	All 148 reactions graded preventable, including contrast and vaccine reactions	Shown descriptively; outlier
Jindal 2023	Causality given as 57%, 41%, 1%, 1% of 148; whole numbers sum to 147	Raw counts to be taken from AMC records
Kumar 2023 (excluded)	Abstract gives 64.70% probable, 85.29% mild, 45.58% preventable; counts give 53/82 (64.6%), 70/82 (85.4%), 37/82 (45.1%)	Noted; study excluded as anticancer-only
Gupta 2025	Abstract: 282 suspected ADRs analysed; Methods: 200 reports	282 are reactions within 200 reports; 200 used
Lhamo 2025	Abstract gives antimicrobials as 33%; Table 2 gives 76 (30%)	Table value used
Singh 2017	Causality categories sum to 231 of 232 reports	One report not classified
Choudhury 2023	Antimicrobial share uses 179 drugs, not 161 reports, as denominator	Drug class not analysed
Imran 2023	Hospital and design not stated; title claims outpatients, data are inpatients only	High risk of bias; sensitivity analysis without it
Imran 2023	Unusual synonym substitution throughout the text (for example guys for males)	Noted; no inference drawn
James 2020 (excluded)	Severity given as 75% mild in Results and 60% in Discussion	Excluded for Naranjo causality

4. Discussion

Principal findings

Across eleven published Indian audits, the share of reports graded probable ranged from about a fifth to more than nine in ten, the severe share from 2% to 18%, and the not-preventable share from none to nearly all. Pooled values (about seven in ten probable and 8% severe) sit near the middle of these ranges but do not represent any one centre.

What this design can and cannot show

Each centre graded its own reports, which differ in drug mix, case mix and reporting culture. The spread across centres is therefore a measure of variation, not of disagreement between graders. Case mix probably explains part of it. Vaccine and contrast reactions, for example, meet none of the modified Schumock-Thornton criteria for preventability unless a previous reaction was documented, yet Jindal 2023 recorded all 20 vaccine and 20 contrast reactions in its series as preventable.[13] Measuring how much of the variation comes from grading practice requires several centres to grade the same set of reports.

Why causality grades vary

For causality, the only feature that clearly separated studies was active surveillance, and it rests on one study. Chandrabhan 2021 graded 22.5% probable against 41.2% to 91.4% in the spontaneous-report studies. One possible explanation is that active surveillance captures reactions before dechallenge is known, which would favour possible over probable, but a single study cannot test this, and that study was also inpatient-only. Jindal 2023, from the authors' own centre, had the second-lowest probable share (41.2%), the lowest not-preventable share (0%) and the second-highest moderate share (83%). There was no evidence that region, inpatient setting or period explained the remaining spread, but the analyses were underpowered.

Why preventability was not pooled

The Schumock-Thornton questions ask whether the drug was appropriate, whether dose and monitoring were correct and whether a known allergy or interaction was overlooked. These need the clinical record, which spontaneous forms rarely carry. All six centres used the same three-category version, so the spread is not an artefact of the scale version. A pooled figure would have been precise-looking and uninformative.

Limitations and the likely direction of bias

Selection bias. The studies are a convenience sample assembled partly from the authors' department and partly from an unlogged search. Its direction cannot be predicted, and it is the main reason every estimate here is provisional.

Single reviewer and conflict of interest. Screening, extraction and appraisal were done once. Two authors wrote Jindal 2023 and the excluded Kumar 2023.[36]

Under-reporting. Spontaneous reporting favours visible, clearly drug-related reactions of at least moderate severity, so the probable and moderate shares probably overstate, and the mild share understates, what occurs in patients.[5]

Back-calculation and few studies. Three studies printed percentages only; the most uncertain cell moved the primary estimate by 0.1 points. With eight to eleven studies, the exploratory analyses have little power and their nominal p values should not guide conclusions.

Implications

For service planning, the ranges matter more than the pooled values: a centre should expect anywhere from a quarter to nearly all of its reports to be graded probable, and roughly 2% to 18% severe. For research, a multicentre study in which several AMCs regrade a common set of reports would show how much of the spread is grading practice. For journals, AMC audits should print one table of raw counts for all three scales.

Appendix A. Extraction sheet

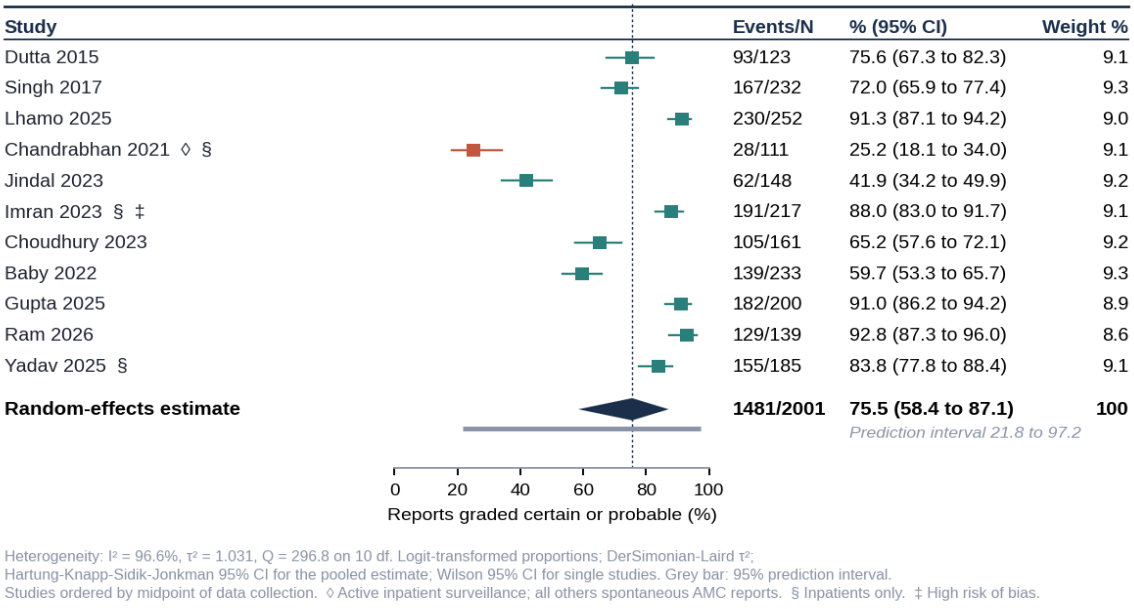
Table A1. Every count used, all eligible studies

Study	N	Certain/ probable/ possible/ other	Mild/ moderate/ severe	Definitely/ probably/ not preventable	Extraction note
Dutta 2015	123	2/91/30/0	NR	NR	Severity reported only as seriousness, so not poolable on Hartwig-Siegel
Singh 2017	232	11/156/64/1	NR	NR	Causality categories sum to 231 of 232; one report unaccounted and placed under other
Lhamo 2025	252	28/202/22/0	150/78/24	30/48/174	Table counts used; abstract gives 33% antimicrobials against 30% in Table 2
Chandrabhan 2021	111	3/25/83/0	92/17/2	NR	Hospitalised patients in medicine, surgery and orthopaedics only
Jindal 2023	148	1/61/84/1	22/123/3	143/5/0	Causality counts back-calculated from rounded percentages (57%, 41%, 1%, 1%); sum is 147, not 148
Imran 2023	217	5/186/26/0	66/111/40	NR	Study site never named; design not stated; all 217 reports are inpatients (79 admissions caused by an ADR, 138 ADRs arising in hospital) despite the title; severity summed across the two groups; text shows heavy synonym substitution
Choudhury 2023	161	8/97/56/0	62/74/25	68/59/34	All counts back-calculated from percentages of 161; antimicrobial share uses drugs, not ADRs, as denominator
Baby 2022	233	2/137/90/4	29/178/26	2/169/62	Severity counts back-calculated from 12.4%, 76.4%, 11.2% of 233
Gupta 2025	200	0/182/16/2	NR	NR	200 reports carrying 282 ADRs; causality reported per report; severity not reported
Ram 2026	139	2/127/10/0	9/124/6	4/0/135	All counts from Table 4
Yadav 2025	185	16/139/27/3	29/143/13	15/40/130	185 ADRs in 177 patients; other causality = 1 unlikely + 2 unclassified

Appendix B. Reports excluded

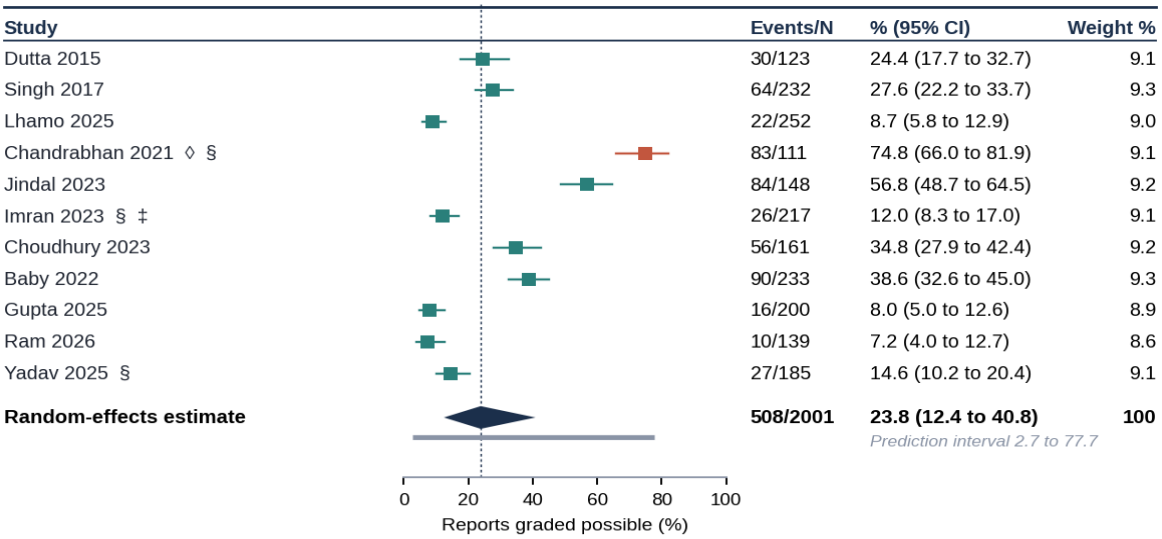
Report	Journal	Site	Reason
Kumar 2023	Cureus 15(9):e44984	Faridkot, Punjab	Anticancer drugs only
Kumar S 2023	Int J Basic Clin Pharmacol 12(1):58	Patna, Bihar	Causality by Naranjo, not WHO-UMC; 32 ADRs only
James 2020	Asian J Pharm Clin Res 13(1)	South India	Causality by Naranjo; severity given as 75% mild in Results and 60% in Discussion
Mohanan 2021	Asian J Pharm Clin Res 14(2)	Thrissur, Kerala	No causality, severity or preventability data reported
Chindhalore 2024	Cureus 16(2):e53706	Nagpur, Maharashtra	Cutaneous ADRs only
Rukmangathen 2020	Perspect Clin Res 11:158	Tirupati, Andhra Pradesh	Antiretroviral drugs only
Hari Sankar 2022	Perspect Clin Res 13:194	Kottayam, Kerala	Antituberculosis drugs only
Singh H 2013	J Glob Infect Dis 5:104	Jagdalpur, Chhattisgarh	Off topic: quality of life on HAART
Kaur K 2021	IP Int J Compr Adv Pharmacol 6(2):79	Faridkot, Punjab	Off topic: KAP on medicine disposal
Jain A 2018	Int J Basic Clin Pharmacol 7(5):1002	Faridkot, Punjab	Off topic: package insert content

Appendix C. Secondary forest plots and exploratory analyses



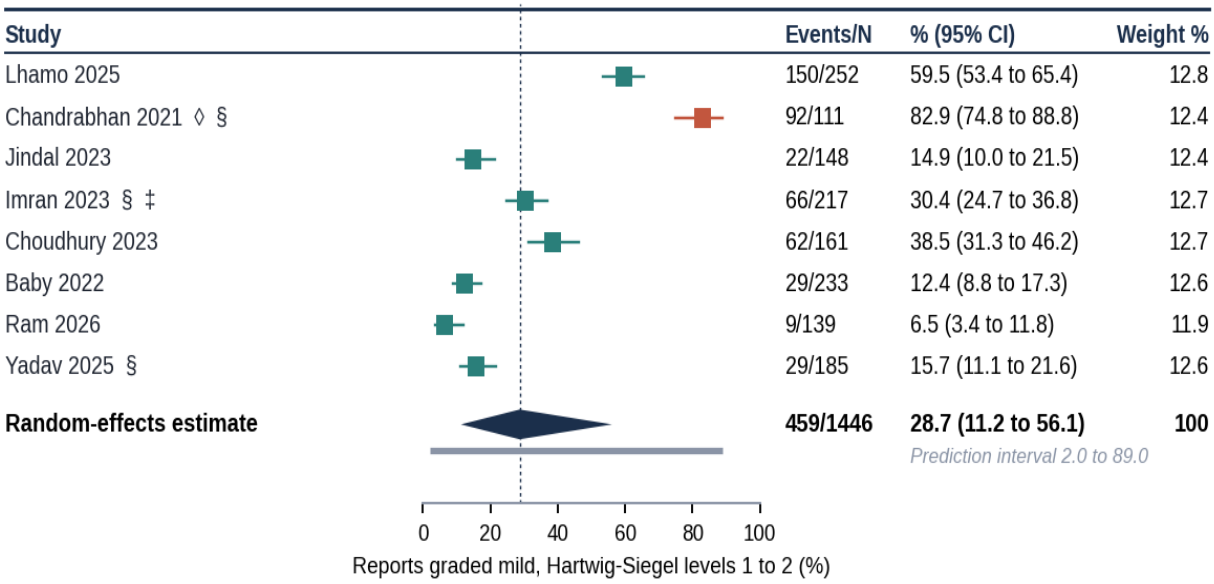
Heterogeneity: I^2 = 96.6%, τ^2 = 1.031, Q = 296.8 on 10 df. Logit-transformed proportions; DerSimonian-Laird τ^2; Hartung-Knapp-Sidik-Jonkman 95% CI for the pooled estimate; Wilson 95% CI for single studies. Grey bar: 95% prediction interval. Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure C1. Certain or probable.



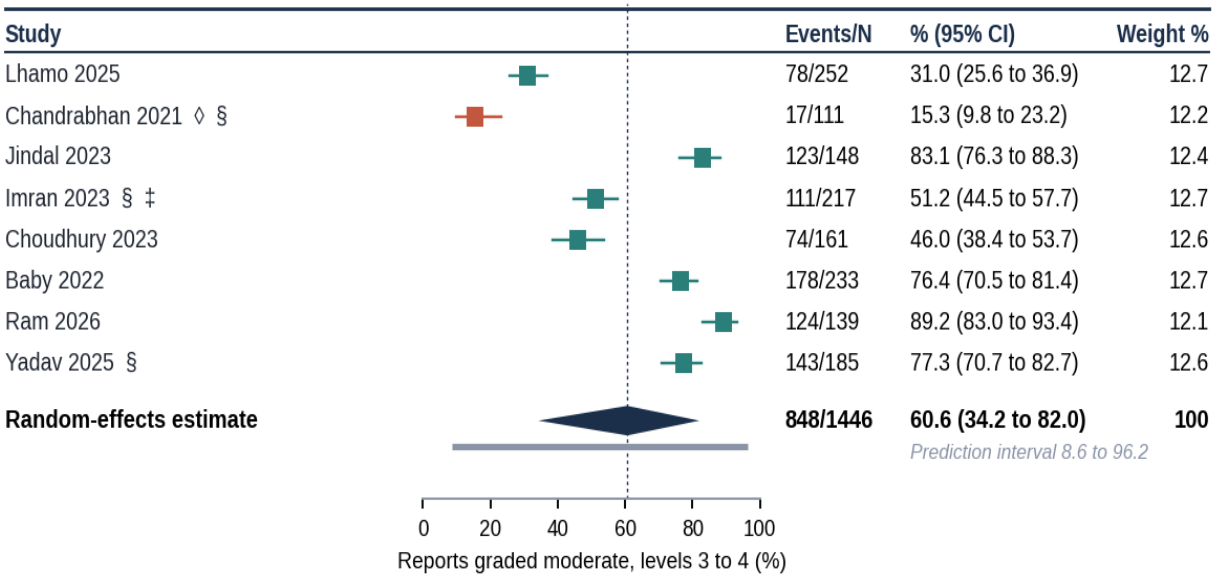
Heterogeneity: I^2 = 96.6%, τ^2 = 1.039, Q = 294.4 on 10 df. Logit-transformed proportions; DerSimonian-Laird τ^2;
Hartung-Knapp-Sidik-Jonkman 95% CI for the pooled estimate; Wilson 95% CI for single studies. Grey bar: 95% prediction interval.
Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure C2. Possible.



Heterogeneity: I^2 = 97.4%, τ^2 = 1.331, Q = 271.8 on 7 df. Logit-transformed proportions; DerSimonian-Laird τ^2;
Hartung-Knapp-Sidik-Jonkman 95% CI for the pooled estimate; Wilson 95% CI for single studies. Grey bar: 95% prediction interval.
Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure C3. Mild.



Heterogeneity: I^2 = 97.4%, τ^2 = 1.161, Q = 274.2 on 7 df. Logit-transformed proportions; DerSimonian-Laird τ^2; Hartung-Knapp-Sidik-Jonkman 95% CI for the pooled estimate; Wilson 95% CI for single studies. Grey bar: 95% prediction interval. Studies ordered by midpoint of data collection. ◊ Active inpatient surveillance; all others spontaneous AMC reports. § Inpatients only. ‡ High risk of bias.

Figure C4. Moderate.

Table S1. Exploratory analyses (not prespecified; 18 tests)

Outcome	North vs rest, %	p	p, Rajasthan moved	Inpatient only vs mixed, %	p	Year slope (logit per year)	p
Probable causality	69.5 vs 71.9	0.844	0.269	63.6 vs 73.2	0.613	+0.05	0.692
Certain or probable	74.2 vs 76.5	0.852	0.328	70.1 vs 77.3	0.711	+0.05	0.712
Possible causality	25.2 vs 22.7	0.835	0.331	29.1 vs 22.2	0.723	-0.05	0.671
Mild severity	46.1 vs 15.9	0.043	0.718	42.1 vs 22.0	0.339	-0.87	0.020
Moderate severity	44.7 vs 74.5	0.072	0.745	46.7 vs 68.4	0.307	+0.81	0.023
Severe	6.3 vs 9.2	0.454	0.840	7.5 vs 8.2	0.881	-0.03	0.922

Subgroups with two studies use DerSimonian-Laird intervals. Meta-regression: DerSimonian-Laird τ^2 with Knapp-Hartung adjustment; midpoint of data collection centred at 2020.

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