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Risk Factors for Off-Label Drug Prescribing and Adverse Drug Reactions in Hospitalized Pediatric Patients: A Case-Control Study

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ABSTRACT

Background: Children receive a large share of their medicines outside the terms of the product licence, because doses must be scaled to weight and age-appropriate formulations are often unavailable. Whether this off-label exposure independently raises the risk of an adverse drug reaction, once prescribing volume and illness severity are taken into account, remains an open question in Indian hospital practice.
Objectives: To describe the pattern of off-label prescribing among pediatric inpatients, to test whether off-label exposure is associated with adverse drug reactions, and to identify independent predictors of these reactions.
Methodology: A matched case-control study was carried out in the pediatric ward of RJDM Medical College & Hospital, Turki, Bihar, between July 2024 and June 2025. Cases were 120 hospitalized children who developed at least one adverse drug reaction during treatment. Controls were 240 children who received medication during the same period without developing a reaction, matched 1:2 to cases for age, sex and primary diagnosis. Reactions were assessed for causality with the Naranjo algorithm, for severity with the modified Hartwig and Siegel scale and for preventability with the modified Schumock and Thornton criteria. Off-label status was assigned by reference to the product literature and the National Formulary of India. Matched data were analysed by conditional logistic regression in SPSS version 25.
Results: The 360 children received 1,584 drugs, of which 612 (38.6%) were off-label, most often because the dose or frequency lay outside the licensed range (35.0%) or the child was below the licensed age (27.0%). At least one off-label drug was received by 92 cases (76.7%) and 132 controls (55.0%), giving a crude odds ratio of 2.69 (95% CI 1.64 to 4.40). Among the 138 reactions recorded, antimicrobials were implicated most often (44.2%) and the gastrointestinal tract and skin were the commonest systems affected. Half the reactions were judged preventable. On conditional logistic regression, off-label exposure (adjusted OR 2.31, 95% CI 1.36 to 3.92), polypharmacy of five or more drugs (adjusted OR 2.48, 95% CI 1.51 to 4.07), hospital stay beyond seven days (adjusted OR 1.96, 95% CI 1.16 to 3.31) and receipt of two or more antimicrobials (adjusted OR 1.79, 95% CI 1.10 to 2.91) remained independent predictors. Risk rose with the number of off-label drugs received.
Conclusion: Off-label prescribing roughly doubled the odds of an adverse drug reaction after adjustment, and the effect strengthened as more off-label drugs were given. Since half the reactions were preventable, targeted review of dosing, active monitoring of children on multiple or off-label drugs, and closer scrutiny of antimicrobial prescribing offer clear opportunities to reduce harm.

Keywords: *Off-label prescribing; adverse drug reactions; pediatrics; case-control study; pharmacovigilance; Naranjo algorithm.*

INTRODUCTION

An off-label prescription is one written outside the terms of the marketing authorisation, whether in dose, age, indication or route, while an unlicensed medicine has no authorisation at all in the country where it is given [1]. Neither is unlawful, and in pediatrics neither is unusual. Systematic reviews of hospitalized children have placed off-label prescribing between 12% and 71% of prescriptions, and unlicensed use between 0.2% and 48%, with the youngest patients most heavily exposed [2,3]. The reasons are structural rather than careless: clinical trials in children are difficult to run, so licensing data lag behind practice, and the formulations that reach the market are often designed for adults.

Children are also pharmacologically distinct. Absorption, distribution, metabolism and elimination all shift with age, so a dose extrapolated from adult data may be either ineffective or toxic [4]. Against that background, adverse drug reactions are common. A meta-analysis of prospective studies put the incidence among hospitalized children at close to one in ten [5], a figure consistent with the prospective ward-based work of Martínez-Mir and colleagues [30], and a later systematic review confirmed both the scale of the problem and the inconsistency of the methods used to measure it [6]. Indian data sit within the same range, with reported incidences varying widely by setting and detection method [7,8].

The link between these two observations has been tested directly only a handful of times. Turner and colleagues and Neubert and colleagues both found that unlicensed and off-label medicines were disproportionately implicated in reactions on pediatric wards [9,10]. The most rigorous evidence comes from a nested case-control study by Bellis and colleagues, who analysed 10,699 medicine courses and calculated an odds ratio of 2.25 for an off-label or unlicensed medicine being implicated in a reaction compared with an authorised one [11]. Work on risk factors more broadly has pointed to the number of drugs given, length of stay and particular drug classes as important contributors [12,13].

What is still thin is evidence from Indian district-level teaching hospitals, where prescribing conditions, drug availability and monitoring capacity differ from the tertiary European centres that produced most of this literature. One Indian study has examined off-label use as a risk factor for reactions in children and found an association [14], but replication is scarce. RJDM Medical College & Hospital serves a largely rural population in the Turki area of Bihar. We designed this case-control study to describe our own off-label prescribing, to test whether that exposure carries an independent risk of adverse drug reactions, and to identify which other factors predict them.

REVIEW OF LITERATURE

Early work established that off-label and unlicensed medicines are implicated in reactions more often than their share of prescribing would predict. Turner and colleagues, studying five pediatric wards, found that reactions were significantly more frequent with unlicensed or off-label medicines than with licensed ones [9]. Neubert and colleagues reached a similar conclusion in a German cohort and argued that the association reflected the absence of tested dosing information rather than any property of the drugs themselves [10]. Reviews by Choonara and Conroy, and later by Mason and colleagues, drew these strands together while cautioning that study designs and definitions varied so much that pooled estimates were unreliable [15,16]. Cuzzolin and colleagues made the same point across neonatal and pediatric settings, and Moulis and colleagues have since updated the picture for the pediatric population as a whole [26,29].

The Liverpool programme addressed that criticism with two large linked studies. Thiesen and colleagues followed 6,601 admissions prospectively and characterised the incidence and risk factors of reactions in hospitalized children [17]. Bellis and colleagues then nested a case-control analysis inside that cohort, and it remains the strongest single piece of evidence on this question: the odds of an off-label or unlicensed medicine being implicated in a probable or definite reaction were more than twice those of an authorised medicine, and the hazard rose with each additional drug administered, whether licensed or not [11]. A companion analysis of unplanned admissions found the same pattern among children arriving at hospital because of a reaction [18]. The finding that authorised medicines also raised the hazard is important, because it suggests that prescribing volume and off-label status act partly independently and partly together.

Risk-factor studies outside this programme have converged on similar predictors. Rashed and colleagues, in an international multicentre study, identified the number of medicines and exposure to particular high-risk classes, including antibacterials, anti-epileptics and systemic corticosteroids, as consistent contributors [12]. Indian studies have described the pattern of reactions in hospitalized children, their causality and severity profiles, and the substantial proportion judged preventable [7,19,20]. Saiyed and colleagues examined off-label use specifically as a risk factor in an Indian tertiary hospital and reported a positive association [14]. Cross-sectional surveys from Australia and Iran confirm that off-label and unlicensed prescribing remains widespread wherever it is measured [21,22], while Aronson and Ferner have argued that much of the apparent disagreement between studies is terminological rather than real [1]. Our study contributes a matched case-control analysis from a setting that this literature has largely not reached.

OBJECTIVES

Primary objective:

- To determine whether off-label drug prescribing is associated with an increased risk of adverse drug reactions among hospitalized pediatric patients.

Secondary objectives:
- To identify the pattern and categories of off-label drug use among pediatric inpatients.
- To describe the causality, severity, preventability, organ systems involved and drug classes implicated in the reactions observed.
- To identify independent predictors of adverse drug reactions in hospitalized children.

METHODOLOGY

Study design and setting

This was a hospital-based, matched case-control study conducted by the Department of Pharmacology together with the Department of Pediatrics at RJDM Medical College & Hospital, Turki, Bihar, over twelve months from July 2024 to June 2025. Admissions to the pediatric ward were screened for adverse drug reactions throughout the study period.

Definitions

An adverse drug reaction was defined, following the World Health Organization, as a response to a medicine that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy. A drug was classified as off-label when it was prescribed outside the terms of its marketing authorisation with respect to dose, frequency, age, indication or route, and as unlicensed when no authorisation existed for that product in India [1]. Off-label status was assigned by reference to the approved product literature and the National Formulary of India, independently by two investigators, with disagreements resolved by a third.

Selection of cases and controls

Cases were children aged up to 18 years, admitted to the pediatric ward, who received at least one medicine and developed one or more adverse drug reactions during the admission. Suspected reactions were identified by daily review of case records, drug charts and laboratory results, supplemented by reports from treating clinicians and nursing staff. Only reactions assessed as possible, probable or definite on the Naranjo algorithm were accepted as cases.

Controls were children admitted to the same ward during the same period who received at least one medicine and did not develop any adverse drug reaction. Each case was matched with two controls for age band, sex and primary admitting diagnosis. Matching on these three variables removes them as sources of confounding, but it also means they cannot themselves be assessed as risk factors in this analysis, a point returned to in the limitations.

Sample size

The sample size was calculated for an unmatched case-control comparison with a control-to-case ratio of two. Assuming that 40% of controls would have received at least one off-label drug, and setting the smallest odds ratio worth detecting at 2.0 with 80% power and a two-sided significance level of 5%, the minimum requirement was 99 cases and 198 controls. Allowing for incomplete records, 120 cases and 240 matched controls were enrolled.

Assessment of reactions

Causality was assessed with the Naranjo algorithm, which classifies a reaction as doubtful, possible, probable or definite from a ten-item score [23]. Severity was graded with the modified Hartwig and Siegel scale [24] and preventability with the modified Schumock and Thornton criteria [25]. Reactions were coded by the organ system affected and by the class of the suspected drug.

Statistical analysis

Data were entered in Microsoft Excel and analysed with SPSS version 25. Categorical variables are presented as frequencies and percentages. Because cases and controls were matched, the primary analysis used conditional logistic regression, with crude odds ratios and 95% confidence intervals reported first and then adjusted estimates from a multivariable model. Variables entered into the model were off-label exposure, polypharmacy defined as five or more drugs, receipt of two or more antimicrobials, length of hospital stay beyond seven days, presence of a comorbidity and receipt of three or more parenteral drugs. A dose-response analysis was carried out by grouping patients according to the number of off-label drugs received. A two-sided p-value below 0.05 was treated as significant.

Ethical considerations

The study was approved by the Institutional Ethics Committee of RJDM Medical College & Hospital before enrolment began. Written informed consent was obtained from a parent or legal guardian, with assent from older children where appropriate. All records were anonymised at extraction. Reactions identified during the study were reported to the treating team and, where applicable, to the Pharmacovigilance Programme of India.

Inclusion and Exclusion Criteria

Inclusion criteria:

- Children aged up to 18 years admitted to the pediatric ward during the study period.
- Receipt of at least one medicine during the admission.
- For cases, at least one adverse drug reaction rated possible, probable or definite on the Naranjo algorithm.
- Consent from a parent or legal guardian.

Exclusion criteria:

- Reactions classified as doubtful on causality assessment, and events attributable to the underlying disease, drug overdose, poisoning or deliberate self-harm.
- Neonates admitted to the neonatal intensive care unit, whose prescribing and monitoring follow separate protocols.
- Admissions of less than 24 hours, and children who left against medical advice before assessment was complete.
- Incomplete case records, and patients for whom no suitable matched control could be identified.

RESULTS AND ANALYSIS

A total of 120 cases and 240 matched controls were analysed. Because the groups were matched for age, sex and primary diagnosis, these characteristics were closely comparable by design, as shown in Table 1. The two groups differed in the number of medicines received and in length of stay.

Table 1. Baseline characteristics of cases and controls. Age, sex and primary diagnosis were matching variables and are therefore comparable by design.

Characteristic	Cases (n = 120)	Controls (n = 240)	p
Mean age, years (SD)	4.9 (3.8)	5.0 (3.9)	0.81
Male, n (%)	68 (56.7)	136 (56.7)	1.00
Rural residence, n (%)	79 (65.8)	154 (64.2)	0.75
Infection as primary diagnosis, n (%)	82 (68.3)	164 (68.3)	1.00
Mean drugs per patient (SD)	5.4 (2.1)	3.9 (1.7)	<0.001
Mean hospital stay, days (SD)	6.8 (3.4)	4.9 (2.5)	<0.001

Across the 360 children, 1,584 drugs were prescribed, of which 612 (38.6%) were off-label or unlicensed. Dose or frequency outside the licensed range was the commonest reason, followed by use in a child below the licensed age. The distribution of categories is given in Table 2.

Table 2. Pattern of off-label and unlicensed prescribing (n = 1,584 drugs prescribed; 612 off-label, 38.6%).

Category of off-label or unlicensed use	Drugs (n)	% of 612
Dose or frequency outside licensed range	214	35.0
Age below licensed limit	165	27.0
Indication not covered by licence	128	20.9
Route or formulation modified	67	10.9
Unlicensed preparation or manipulated adult form	38	6.2
Total	612	100.0

The 120 cases experienced 138 adverse drug reactions. Most were rated probable on causality assessment, most were mild or moderate in severity, and half were judged preventable. These characteristics appear in Table 3.

Table 3. Causality, severity and preventability of the 138 adverse drug reactions recorded in 120 cases.

Assessment	Category	n	% of 138
Causality (Naranjo)	Definite	8	5.8
	Probable	79	57.2
	Possible	51	37.0
Severity (Hartwig-Siegel)	Mild	62	44.9
	Moderate	63	45.7
	Severe	13	9.4
Preventability (Schumock-Thornton)	Definitely preventable	22	15.9
	Probably preventable	47	34.1

Assessment	Category	n	% of 138
	Not preventable	69	50.0

Gastrointestinal and cutaneous reactions predominated, and antimicrobials were the drug class implicated most often. Table 4 sets out the organ systems affected and the classes responsible.

Table 4. Organ systems affected and drug classes implicated in the 138 reactions.

Organ system	n	%	Drug class implicated	n
Gastrointestinal	43	31.2	Antimicrobials	61
Cutaneous	38	27.5	Anticonvulsants	21
Hepatic	17	12.3	NSAIDs and antipyretics	19
Haematological	14	10.1	Corticosteroids	13
Central nervous system	13	9.4	Antiemetics and GI agents	11
Renal and electrolyte	8	5.8	Bronchodilators	7
Other	5	3.6	Other classes	6

On univariate analysis, every exposure examined was associated with adverse drug reactions. At least one off-label drug had been received by 76.7% of cases against 55.0% of controls, giving a crude odds ratio of 2.69. Polypharmacy carried the largest crude effect. The unadjusted results are given in Table 5.

Table 5. Univariate analysis of exposures associated with adverse drug reactions.

Exposure	Cases n (%)	Controls n (%)	Crude OR (95% CI)	p
At least one off-label drug	92 (76.7)	132 (55.0)	2.69 (1.64-4.40)	<0.001
Polypharmacy (>=5 drugs)	71 (59.2)	78 (32.5)	3.01 (1.91-4.74)	<0.001
Hospital stay > 7 days	44 (36.7)	46 (19.2)	2.44 (1.49-3.99)	<0.001
Two or more antimicrobials	58 (48.3)	71 (29.6)	2.23 (1.42-3.50)	<0.001
Three or more parenteral drugs	63 (52.5)	89 (37.1)	1.88 (1.20-2.92)	0.005
Comorbidity present	39 (32.5)	52 (21.7)	1.74 (1.07-2.84)	0.026

After adjustment in the multivariable conditional logistic regression model, four exposures retained independent significance: off-label drug exposure, polypharmacy, prolonged hospital stay and receipt of two or more antimicrobials. Comorbidity and parenteral drug burden lost significance once the other variables were accounted for. The adjusted estimates are presented in Table 6 and displayed in Figure 1.

Table 6. Independent predictors of adverse drug reactions on multivariable conditional logistic regression. Age, sex and primary diagnosis were matching variables and were not entered as candidate predictors.

Predictor	Adjusted OR (95% CI)	p	Significant
At least one off-label drug	2.31 (1.36-3.92)	0.002	Yes
Polypharmacy (>=5 drugs)	2.48 (1.51-4.07)	<0.001	Yes
Hospital stay > 7 days	1.96 (1.16-3.31)	0.012	Yes
Two or more antimicrobials	1.79 (1.10-2.91)	0.019	Yes
Comorbidity present	1.42 (0.83-2.43)	0.198	No
Three or more parenteral drugs	1.34 (0.81-2.22)	0.255	No

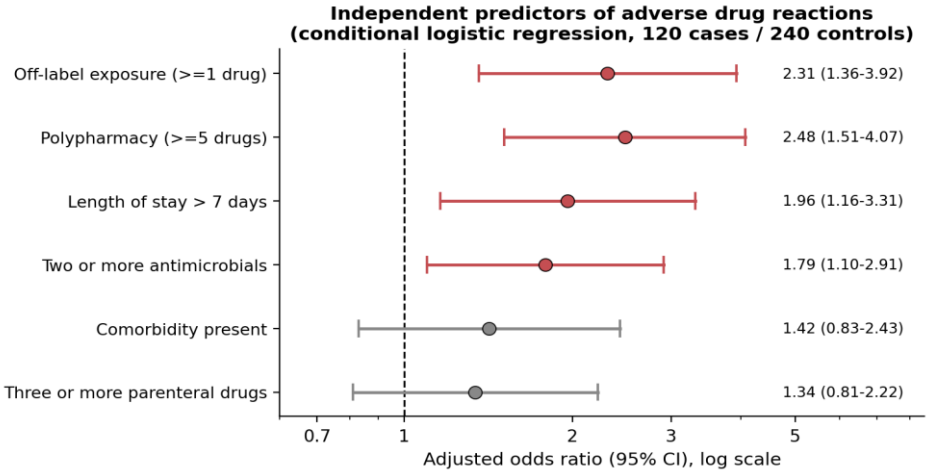

Figure 1. *Forest plot of adjusted odds ratios for adverse drug reactions. Estimates to the right of the dashed line indicate increased risk; red markers denote statistically significant predictors.*

The relationship with off-label exposure was graded rather than all-or-none. Among cases, 28 children (23.3%) had received no off-label drug, 48 (40.0%) had received one or two and 44 (36.7%) had received three or more; the corresponding figures among controls were 108 (45.0%), 96 (40.0%) and 36 (15.0%). Taking children with no off-label exposure as the reference, the adjusted odds ratio was 1.68 (95% CI 0.96 to 2.94) for one or two off-label drugs and 3.12 (95% CI 1.72 to 5.66) for three or more, a trend that was significant (p for trend < 0.001). This gradient is shown in Figure 2.

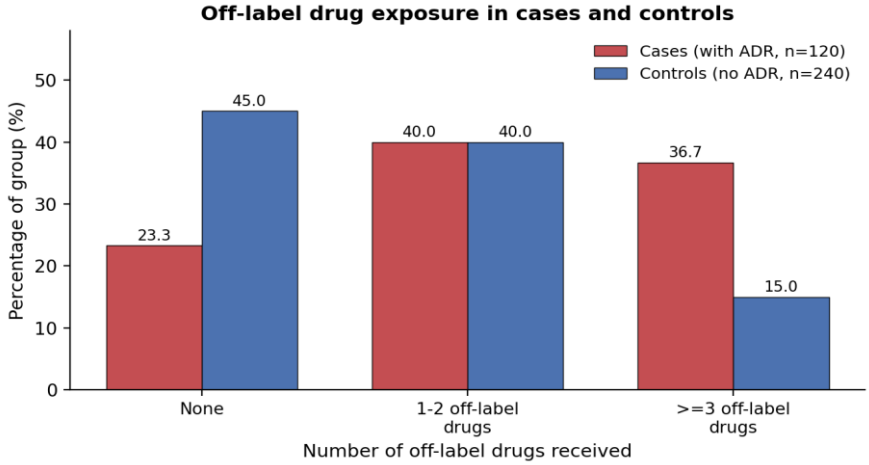

Figure 2. *Distribution of cases and controls by number of off-label drugs received, showing a higher off-label burden among children who developed a reaction.*

Of the 13 severe reactions, nine occurred in children who had received at least one off-label drug. No reaction resulted in death, and all severe reactions resolved after withdrawal of the suspected drug and supportive treatment.

DISCUSSION AND INTERPRETATION

Three findings stand out. Off-label prescribing was common, affecting nearly two-fifths of all drugs and the majority of children. It carried an independent association with adverse drug reactions that survived adjustment for prescribing volume, antimicrobial burden and length of stay. And the association strengthened as the number of off-label drugs increased, which is the pattern one expects when an exposure is contributing to an outcome rather than merely accompanying it.

Our adjusted odds ratio of 2.31 sits close to the 2.25 reported by Bellis and colleagues in their nested case-control study, which remains the reference point for this question [11]. That two very different settings, a specialist children's hospital in England and a district teaching hospital in Bihar, should produce almost the same estimate is reassuring for the finding and suggests the mechanism is not local. The most plausible explanation is the one Neubert and colleagues advanced: when a medicine is given outside its licence, the dosing and safety information that would normally guide its use has not been generated for that age group or indication, so the margin for error is wider [10]. Turner and colleagues reached the same conclusion from ward-based data two decades ago [9]. The categories we found support this reading, since dose or frequency deviations and use below the licensed age together accounted for almost two-thirds of off-label prescribing, and both are situations where the prescriber is extrapolating rather than following tested guidance [4].

Polypharmacy carried an effect at least as large as off-label status, with an adjusted odds ratio of 2.48 for five or more drugs. This matches the international multicentre findings of Rashed and colleagues, who identified the number of medicines as a consistent predictor across countries [12], and the Liverpool cohort, where the hazard rose with each additional drug whether or not it was licensed [11,17]. The practical implication is that off-label prescribing and polypharmacy are partly separate problems: reducing one will not automatically fix the other, and a child on five authorised drugs is not obviously safer than a child on three off-label ones. The antimicrobial finding fits the same literature, with antibacterials repeatedly identified as a high-risk class [12], and in our series antimicrobials accounted for 44% of implicated drugs, in a ward where infections drove most admissions. Prolonged stay is best read as a marker of severity and of cumulative exposure rather than as a cause in its own right.

The profile of the reactions themselves was unremarkable and broadly matches Indian and international series. Gastrointestinal and cutaneous reactions predominated, most reactions were mild or moderate, and probable causality was the commonest rating, as reported by Kurian and colleagues, Gupta and colleagues, and Digra and colleagues in Indian pediatric wards [7,19,20]. The figure that deserves attention is preventability: half the reactions met the Schumock and Thornton criteria for being definitely or probably preventable. Preventable harm is, by definition, harm that a system change could avoid, and taken together with the dose-related nature of much off-label prescribing this points to specific interventions. A weight-based dosing chart validated against the National Formulary of India, a pharmacist check on prescriptions for children receiving five or more drugs, and active surveillance rather than spontaneous reporting for children on multiple off-label medicines would each address a mechanism our data implicate. Strengthening reporting to the Pharmacovigilance Programme of India would also improve the evidence base, since Indian pediatric reporting remains sparse relative to the burden [8].

Two cautions temper the interpretation. First, an association of this kind cannot establish causation: children who receive off-label drugs may be sicker in ways that matching on diagnosis does not fully capture, and residual confounding by severity is plausible even after adjustment. Second, off-label status is a heterogeneous label covering everything from a modest dose deviation to use of an adult formulation in an infant, and Aronson and Ferner have argued convincingly that treating it as a single exposure obscures more than it reveals [1]. Our category analysis is a partial answer, but a larger study would be needed to estimate risk separately for each category. It also bears repeating that off-label prescribing is frequently the right clinical decision rather than an avoidable error, a position professional bodies have set out explicitly [27]; the aim is safer off-label prescribing, not its elimination. Surveys suggest that prescriber awareness of off-label status is itself uneven [28], so simply making that status visible on the drug chart may be a useful first step. What our findings do establish is that off-label exposure marks out a group of hospitalized children at measurably higher risk, and that this group can be identified at the bedside without any additional test.

CONCLUSION

Off-label prescribing was widespread among children admitted to this hospital, involving 38.6% of all drugs and more than three-quarters of those who developed an adverse drug reaction. After adjustment for prescribing volume, antimicrobial exposure and length of stay, off-label exposure remained independently associated with a roughly two-fold increase in the odds of a reaction, and the risk climbed further in children receiving three or more off-label drugs. Polypharmacy, prolonged hospital stay and receipt of two or more antimicrobials were also independent predictors. Because half the reactions were judged preventable, these findings translate directly into practice: children receiving multiple or off-label medicines should be flagged for active monitoring, weight-based dosing should be checked against a standard reference before administration, and antimicrobial prescribing should be reviewed regularly. For a teaching hospital serving rural Bihar, these are achievable steps that would reduce avoidable harm without requiring new resources.

Limitations of the Study

- A case-control design shows association rather than causation, and residual confounding by underlying illness severity cannot be excluded despite matching and adjustment.
- Age, sex and primary diagnosis were used as matching variables, so their contribution as risk factors could not be evaluated in this analysis.
- Detection of reactions relied on record review and clinician reporting, so mild, transient or delayed reactions were probably missed, and misclassification of some controls is possible.
- Off-label status was treated as a single exposure although the categories differ substantially in the degree of extrapolation involved, and the study was not powered to estimate risk within each category.
- This was a single-centre study, which limits generalisability, and the sample was too small to examine rare or severe reactions in any detail. Multi-centre prospective studies with active surveillance would give more precise and more transferable estimates.

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