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PAIR-LEVEL DRUG–DRUG INTERACTION EXPOSURE AND ORDINAL CLINICAL OUTCOMES IN CHILDREN HOSPITALIZED WITH PNEUMONIA: PROTOCOL FOR A PROSPECTIVE MULTICENTRE COHORT STUDY IN PESHAWAR, PAKISTAN

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Abstract

Introduction: *Children hospitalized with pneumonia are usually treated with more than one drug, and potential drug–drug interactions (DDIs) are a plausible contributor to poor outcome. A retrospective pilot of 180 children found no association between documented DDI level and treatment outcome, but its interval excluded only moderate or larger associations, interactions were mostly absent or minor (none severe), DDI level was a global clinician rating, and an ordinal outcome was analyzed with a linear model. This protocol describes a prospective study designed to address these limitations.*

Methods and analysis: *A prospective, multicentre, observational cohort study will be conducted in several tertiary care hospitals in Peshawar, Pakistan. Consecutive children aged 2 months to 12 years admitted with clinically diagnosed pneumonia and receiving two or more concurrent drugs will be enrolled (proposed target 500). Every concurrent drug pair will be screened against a single interaction reference by two pharmacists blinded to outcome, giving pair-level exposure data (highest severity, number of interacting pairs, days of exposure). The primary outcome is a four-level ordinal outcome at discharge (recovered, improved, ICU transfer, death). The primary analysis is a proportional-odds regression adjusted for comorbidity, age, illness severity, number of concurrent drugs, antibiotic regimen and hospital. Secondary analyses use a time-to-event model with time-varying exposure. The sample size gives about 83% power to detect a small effect (Cohen's $f^2 = 0.02$).*

Ethics and dissemination: *Approval will be sought from the institutional ethical review committee and the participating hospitals, with written informed consent from parents or guardians. Results will be reported following STROBE and published in a peer-reviewed journal.*

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1. Background and Rationale

Pneumonia is a leading cause of hospitalization and death in children worldwide.[1] Treatment in hospital typically combines several drugs, and potential DDIs among hospitalized children have been described in large pediatric datasets.[2] Interactions are plausible contributors to poor outcome and are potentially preventable through pharmacist review, yet few studies have examined whether the level of interaction in a regimen is associated with clinical outcome in pediatric pneumonia.

We recently analyzed a retrospective pilot cohort of 180 children aged 2 months to 12 years hospitalized with pneumonia at tertiary care hospitals in Peshawar. Documented DDI level was none in 127 (70.6%), minor in 34 (18.9%) and moderate in 19 (10.6%); no severe interaction was recorded. In a multiple linear regression with comorbidity, DDI level was not a significant predictor of treatment outcome (B = −0.084, 95% CI −0.256 to 0.088; p = 0.340). The standardized interval (−0.216 to 0.074) excluded associations larger than about 0.22 standard deviations, and the sample had 80% power for $f^2 \geq 0.044$ but only about 47% power for a small effect ($f^2 = 0.02$). Small associations and rare serious events could therefore not be excluded.

The pilot also exposed design limitations that a prospective study can address directly (Table 1).

Table 1. Limitations of the retrospective pilot and the corresponding design response in this protocol.

Pilot limitation	Design response in this protocol
Narrow exposure range (none 70.6%, minor 18.9%, moderate 10.6%, severe 0%)	Multicentre consecutive enrolment; pair-level severity grading; the number of children at higher severity will be monitored during recruitment
DDI level was a global clinician rating	Every concurrent drug pair screened against one fixed interaction reference by two pharmacists, blinded to outcome, with adjudication
Ordinal outcome analyzed as interval-scaled	Proportional-odds model as primary analysis; time-to-event model for ICU transfer or death
No adjustment for illness severity, age, antibiotic choice or number of drugs	These variables are collected prospectively and entered in the primary model
Retrospective, single-city convenience sample	Prospective consecutive enrolment at several hospitals
About 47% power for a small effect	Sample size based on $f^2 = 0.02$ with 80% power or more

2. Aim, Objectives and Hypotheses

Primary objective. To estimate the association between the highest level of DDI exposure during hospitalization and the ordinal treatment outcome at discharge in children with pneumonia, adjusted for comorbidity, age, illness severity, number of concurrent drugs, antibiotic regimen and hospital.

Secondary objectives. (a) To estimate the association of the number of interacting drug pairs and the number of exposure days with outcome. (b) To estimate the association of DDI exposure with time to ICU transfer or death. (c) To compare length of hospital stay by DDI exposure. (d) To describe the most frequent interacting drug pairs and their severity. (e) To describe suspected interaction-related adverse events and their causality.

Hypothesis. The null hypothesis is that DDI exposure is not associated with treatment outcome. Because a non-significant result cannot confirm it, findings will be interpreted from the confidence interval and the minimum

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detectable effect rather than from the p-value alone.

3. Methods and Analysis

3.1 Study design and setting

This is a prospective, multicentre, observational cohort study conducted in the pediatric wards (and, where applicable, pediatric intensive care units) of at least three tertiary care hospitals in Peshawar, Pakistan. The protocol follows the STROBE statement.

3.2 Participants

Inclusion criteria: age 2 months to 12 years; clinical diagnosis of pneumonia made by the treating physician; receipt of two or more concurrent drugs during admission; written informed consent from a parent or guardian.

Exclusion criteria: admission for a primary diagnosis other than pneumonia; transfer from another facility after more than 48 hours of inpatient treatment, because earlier drug exposure cannot be fully observed; unavailable treatment charts.

3.3 Sample size

The sample size was derived from the pilot's sensitivity analysis, using the noncentral F distribution for the test of a single predictor in a linear model with up to eight predictors (α = 0.05). Table 2 gives the number of evaluable children required for effects of different size. A small effect (f^2 = 0.02, partial correlation of about 0.14) requires 395 evaluable children for 80% power and 528 for 90% power (Figure 1).

Table 2. Evaluable sample size needed to detect a single-predictor effect (two-sided α = 0.05).

Cohen's f^2	Partial r	80% power	90% power	80% power, inflated 15%
0.02 (small)	0.14	395	528	465
0.03	0.17	264	353	311
0.04	0.20	199	265	235

Inflation allows for 15% of children with incomplete data (proposed). Pilot (n = 180) for comparison: 80% power only for $f^2 \geq 0.044$.

We propose to enrol **500 children**. Allowing for 15% incomplete records, about 425 children would be evaluable, giving about 83% power for f^2 = 0.02. If the pilot proportions hold, the cohort would include about 147 children with any interaction (29.4%) and about 53 with a moderate interaction (10.6%). These are approximations: the calculation treats the exposure as continuous and does not model the ordinal outcome or hospital clustering. Before enrolment begins, the pilot's outcome distribution will be tabulated and used in a simulation check of power for the proportional-odds model.

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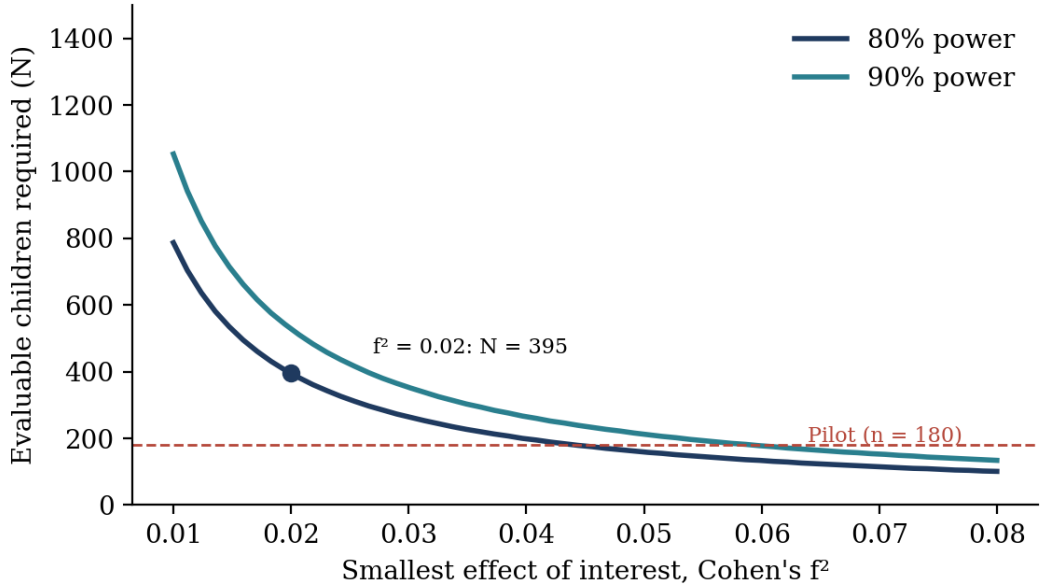


Figure 1. Evaluable sample size required to detect a single-predictor effect of a given size (Cohen's f^2) with 80% and 90% power ($\alpha = 0.05$), compared with the pilot sample of 180 children.

3.4 Exposure assessment

For each child, the drugs administered (name, dose, route, start and stop dates) will be abstracted daily from treatment charts. Every pair of concurrently administered drugs will be screened against one recognized drug-interaction reference, fixed before enrolment (for example, Lexicomp or Micromedex), and classified by severity as minor, moderate or major. Two pharmacists will classify pairs independently and blind to outcome; disagreements will be resolved by a third pharmacist, and inter-rater agreement will be reported (Cohen's kappa).

The primary exposure is the highest interaction severity during the stay (none, minor, moderate, major), which preserves the ordered 0–2 scale used in the pilot and extends it. Secondary exposures are the number of interacting pairs and the cumulative number of exposure days. The interacting pairs themselves will be tabulated so that frequent or high-risk combinations can be described.

3.5 Outcomes

Primary outcome: the worst outcome during the hospital stay, recorded on a four-level ordinal scale ordered from best to worst: recovered, improved, ICU transfer, death. Operational definitions of each level will be fixed in the data dictionary before enrolment.

Secondary outcomes: time from admission to ICU transfer or death (censored at discharge); length of stay; and suspected interaction-related adverse events, with causality assessed using a standard algorithm such as the Naranjo scale.[4]

3.6 Covariates

Covariates are age, sex, comorbidity, illness severity at admission (using the pneumonia severity classification applied in the participating hospitals), initial antibiotic regimen, hospital and the number of concurrent drugs. The last is a key confounder, because children who receive more drugs are more likely to have an interaction and are also likely to be sicker.

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3.7 Data collection

Table 3. Schedule of data collection.

Time point	Data collected
Admission	Eligibility, consent, demographics, comorbidity, illness severity, initial regimen
Daily during stay	Drugs administered (name, dose, route, dates), ICU transfer, clinical events, suspected adverse events
Discharge or death	Outcome category, date of discharge or death, length of stay
After discharge (data cleaning)	Pair-level interaction screening by two blinded pharmacists; adjudication; double data entry and range checks

3.8 Statistical analysis

Continuous variables will be summarized as mean (SD) or median (IQR) and categorical variables as counts and percentages. The primary analysis is a proportional-odds ordinal logistic regression of the four-level outcome on the highest interaction severity, adjusted for the covariates in section 3.6, with hospital as a fixed effect. Results will be reported as odds ratios with 95% CIs. The proportional-odds assumption will be checked with a Brant test[5] and graphically; if it is violated, a partial proportional-odds model or separate binary logistic models at each cut-point will be used.

Secondary analyses are: (i) a linear model comparable with the pilot, to allow direct comparison; (ii) a Cox model for time to ICU transfer or death with interaction exposure as a time-varying covariate, because defining exposure as the highest level over the whole stay would otherwise introduce immortal-time bias; and (iii) models for the number of interacting pairs and exposure days. Missing data will be described; if more than 5% of values are missing, multiple imputation will be used, with a complete-case analysis as sensitivity analysis.[6]

The study has a single primary hypothesis, so no adjustment for multiplicity is planned for the primary analysis. Interpretation will rest on effect estimates, CIs and the minimum detectable effect, and non-significant findings will be described in terms of the effect sizes they exclude.

3.9 Bias and confounding

Selection bias is limited by consecutive enrolment. Information bias is limited by standardized pair-level screening by blinded assessors. Confounding by indication, in which sicker children receive more drugs and have worse outcomes, is addressed by adjustment for illness severity, comorbidity and the number of concurrent drugs; residual confounding remains possible. If the study pharmacists identify a clinically significant interaction, they will notify the treating team according to hospital policy, and that notification will be recorded as a variable so that its influence on outcome can be examined.

3.10 Ethics approval, consent and confidentiality

The protocol will be submitted to the institutional ethical review committee and to the administration of each participating hospital before enrolment. Written informed consent will be obtained from a parent or guardian, with assent from the child where appropriate. Data will be identified by study number only and stored securely with restricted access. The study does not alter clinical care.

3.11 Dissemination

Results will be submitted for publication in a peer-reviewed journal regardless of the direction of findings and reported following STROBE. De-identified data will be available from the corresponding author on reasonable request.

4. Discussion

The pilot analysis could say only that moderate or larger linear associations between documented DDI level and outcome were unlikely. This protocol is designed to produce a more informative answer by widening the exposure range, measuring exposure at the level of the drug pair, using a model that fits the outcome scale, and providing the sample size needed to detect a small effect. The principal threats to its value are the rarity of severe

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interactions, the rarity of serious outcomes and confounding by indication. The first two are managed by reporting the observed distributions during recruitment and by using time-to-event methods; the third is managed by adjustment and cannot be eliminated in an observational design.

Declarations

Ethics approval and consent to participate. The data used for illustration were obtained under approval from the institutional ethical review committee and the administration of the participating hospitals; individual consent was waived for this retrospective record review and all data were anonymized.

Consent for publication. Not applicable.

Availability of data and materials. The dataset is available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Strengths and limitations of this study

- Prospective, consecutive enrolment across several hospitals, designed to widen the range of interaction exposure seen in the pilot.
- Pair-level, reference-based interaction screening by two blinded pharmacists replaces a global clinician rating.
- The ordinal outcome is analyzed with a proportional-odds model, and ICU transfer or death with a time-to-event model, instead of a linear model.
- The sample size is derived from the pilot's sensitivity analysis and is powered for a small effect.
- Observational design: residual confounding by indication cannot be excluded, and severe interactions may still be too rare to study separately.

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