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Reactogenicity, persistent symptom clusters, causal attribution, and interference with daily activities after COVID-19 vaccination in Bangladesh

Md. Hazrat Ali
Mawlana Bhashani Science and Technology University
Shabnur Akter
Mawlana Bhashani Science and Technology University
Farjana Afrin Koasha
Mawlana Bhashani Science and Technology University
Mohammad Shaon Mia
shaonahmed9801@gmail.com

Bangladesh Agricultural University
Asma Khatun
Mawlana Bhashani Science and Technology University
Faijun Nahar Mim
Mawlana Bhashani Science and Technology University
Nigar Sultana
Mawlana Bhashani Science and Technology University
Ekram Hossain Emon
Sylhet Agricultural University
Syed Billal Hossain
University of Science and Technology Chittagong
Mohammad Mosarof Hossain
Sylhet Agricultural University

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Authors
Md. Hazrat Ali[1], Shabnur Akter[1], Farjana Afrin Koasha[1], Mohammad Shaon Mia[2*], Asma Khatun[1], Faijun Nahar Mim[1], Nigar Sultana[3,4], Ekram Hossain Emon[5], Syed Billal Hossain[6,7], and Mohammad Mosarof Hossain[8]

Affiliations
[1]Department of Statistics, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh
[2]Department of Agricultural and Applied Statistics, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh
[3]Department of Mathematics, Mawlana Bhashani Science and Technology University, Tangail, Dhaka, Bangladesh
[4]Applied Mathematics, North Carolina State University, Raleigh, NC, USA
[5]Department of Agricultural Economics and Policy, Sylhet Agricultural University, Sylhet-3100, Bangladesh
[6]Department of Public Health, University of Science and Technology Chittagong, Chattogram-4202, Bangladesh
[7]Department of Public Health, Daffodil International University, Dhaka-1341, Bangladesh
[8]Department of Coastal and Marine Fisheries, Sylhet Agricultural University, Sylhet-3100, Bangladesh

Author email addresses
Md. Hazrat Ali: hazratju01767@gmail.com
Shabnur Akter: shabnuraktermbstu@gmail.com
Farjana Afrin Koasha: farjana.koasha1123@gmail.com
Mohammad Shaon Mia: shaonahmed9801@gmail.com
Asma Khatun: sumaiyaasma9@gmail.com
Faijun Nahar Mim: faijun2005@yahoo.com
Nigar Sultana: nigarsultana@mbstu.ac.bd; nsultan4@ncsu.edu
Ekram Hossain Emon: eemon.aep@gmail.com
Syed Billal Hossain: sbh.raaj@gmail.com
Mohammad Mosarof Hossain: mosarofmh.cmf@sau.ac.bd

Corresponding author
Mohammad Shaon Mia
Department of Agricultural and Applied Statistics, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh
Email: shaonahmed9801@gmail.com

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Abstract

Concern about post-vaccination symptoms influences vaccine confidence, yet safety studies seldom examine how symptoms co-occur or how recipients interpret them. This study aimed to examine whether acute reactions, persistent symptom clusters, and attribution of symptoms to vaccination were associated with interference with daily activities. In a retrospective cross-sectional study, 450 vaccinated people in Tangail District, Bangladesh, were selected by purposive sampling with quotas and interviewed face-to-face between May and August 2026 using a pretested, structured Bangla questionnaire. Participants recalled first-week symptoms after dose one, problems lasting over one month, whether they attributed symptoms to vaccination, and any interference with daily activities. Associations were estimated by structural equation modelling for categorical data. Stronger acute reactions were associated with a greater persistent somatic–cognitive and allergic-type burden ($\beta = 0.624$ and 0.558), whereas sociodemographic and vaccine characteristics explained 8.0% of the variance in acute reactions. Both clusters were associated with stronger attribution, and attribution was associated with interference ($\beta = 0.497$), accounting statistically for 42-45% of each cluster's association with interference. Alternative orderings fitted equally well, so the direction of these associations remains unresolved. Prospective studies with validated measures and a comparison group are needed before appraisal-focused interventions are considered.

Keywords: COVID-19; vaccination; reactogenicity; causal attribution; symptom clusters; structural equation modelling

Introduction

Immunisation was central to the durable containment of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Messenger RNA, protein subunit, viral vector, and inactivated vaccines provided substantial protection against severe disease, hospitalisation, and death,[2-4] and vaccination is estimated to have prevented 14.4 million deaths in 185 countries and territories in its first year.[5] Perceived safety nevertheless remains a principal influence on acceptance,[6] and fear of side effects continues to depress uptake.[7,8] Such hesitancy, defined as delay in acceptance or refusal of vaccination despite available services, is complex and context-specific.[9] In Bangladesh, coverage rose after the national campaign began in early 2021, yet uncertainty about safety remains the most frequently reported reason for hesitancy,[10,11] and surveys report side effects in 39% to 91% of vaccinated people, rising to about 80% after mRNA vaccines.[12,13] Continued monitoring of adverse events is therefore needed to inform immunisation policy.[14]

Pivotal trials described COVID-19 vaccine reactogenicity as short-lived, mild-to-moderate injection-site pain, fatigue and headache, with serious adverse events rare and similar in frequency in vaccine and placebo groups;[2,3] pooled reviews and nationwide analyses confirmed that serious events were uncommon.[15,16] Reactogenicity reflects the inflammatory response to vaccination, and both its intensity and its perception are shaped by host characteristics, vaccine composition and the vaccination setting.[17,18] Its consequences are not trivial: among 8375 health-care workers, nearly one in four vaccinations led to at least one day of work loss,[19] and systemic reactions are more frequent after previous infection,[20] which is substantially under-ascertained in Bangladesh.[21]

Three gaps remain. First, most evidence comes from trial or clinical settings, with few data from real-world populations with diverse risk profiles.[12,22] Second, symptoms persisting

beyond the acute window are poorly characterised, especially in low- and middle-income countries (LMICs).[23] Some recipients report fatigue, cognitive complaints, pain and dysautonomic symptoms lasting months,[24] a presentation difficult to distinguish from long COVID,[25] background morbidity and recall.[26] Third, adverse events are usually listed symptom by symptom against single-event case definitions[27] and compared with demographic variables one at a time, although symptoms tend to co-occur.

Symptoms alone also give an incomplete picture of their consequences. In placebo arms of COVID-19 vaccine trials, 35.2% of participants reported systemic adverse events after the first injection, equivalent to about three-quarters of the systemic events after active vaccination,[28] with symptom profiles resembling those of active arms.[29] Vaccine concern and health anxiety predict self-reported adverse events,[30] and vaccine-hesitant individuals report more, and more severe, events.[31] This evidence shows that expectations can precede and shape symptom reports. Beliefs about vaccine causation may therefore both follow and generate symptoms, yet attribution is rarely measured in vaccine safety research, and its relationship to interference with daily activities has not been quantified.

The objective of this study was to examine how acute reactogenicity, persistent symptom clusters and the attribution of symptoms to vaccination were jointly associated with interference with daily activities among vaccinated people in Bangladesh. We hypothesised that stronger acute reactogenicity would be associated with a greater burden of persistent symptoms, which in turn would be associated with interference with daily activities, both directly and indirectly through stronger causal attribution. Sociodemographic and vaccination characteristics were examined as correlates of acute reactogenicity and persistent symptoms. Because the design was cross-sectional, the hypothesis concerned the pattern of associations rather than causal effects, and alternative orderings were examined. An extended background is provided in Supplementary Note S1.

Methods

Study design and reporting

A retrospective cross-sectional study was conducted among people who had received at least one dose of a COVID-19 vaccine. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies;[32] the completed checklist is given in Supplementary Table S17 (Appendix E).

Conceptual framework

Three theoretical positions informed the model. The symptom cluster concept defines a cluster as two or more concurrent, related symptoms forming a group that is relatively distinct from other clusters and may share an underlying dimension without necessarily sharing the same aetiology.[33] Clusters matter for outcomes; for example, a pain, fatigue and sleep-insufficiency cluster was associated with poorer functional status during chemotherapy.[34] This concept provided the measurement layer, in which post-vaccination complaints were treated as indicators of latent constructs. The theory of unpleasant symptoms provided the outcome layer: co-occurring symptoms may potentiate one another, and their combined effect is expressed in performance of ordinary activities.[35] Structural equation modelling (SEM) has been used to link symptom clusters with health-related quality of life in chronic obstructive pulmonary disease;[36] to our knowledge, this approach has not been applied to post-vaccination symptoms. The common-sense model of self-regulation provided the appraisal layer: people's representations of bodily sensations, including their perceived cause, shape emotional and behavioural responses,[37] a proposition supported meta-analytically.[38] Attribution was therefore placed between persistent symptoms and interference (Fig. 1); because representations can also precede symptom reports, this ordering is one of several compatible with the data and was tested against alternatives.

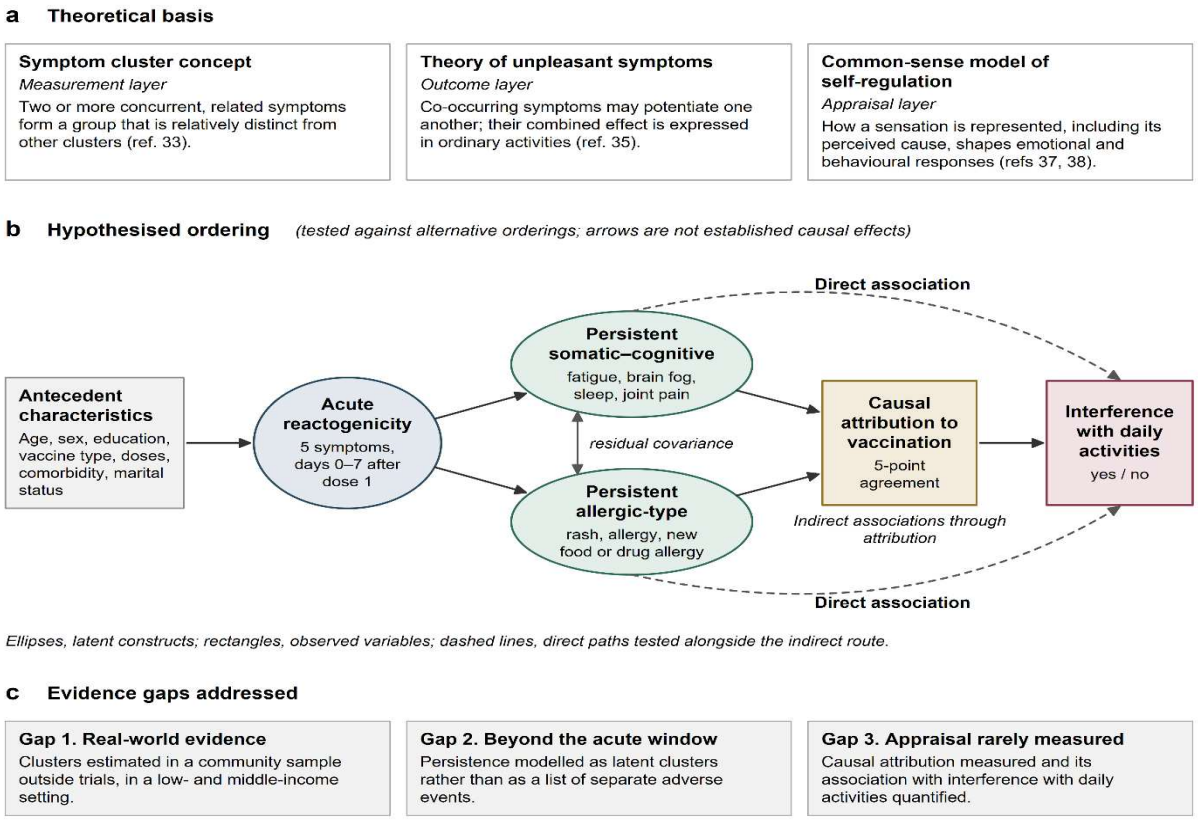


Figure 1 Conceptual framework: The upper band summarises the three theories informing the model; the middle band shows the hypothesised ordering of associations linking antecedent characteristics, acute reactogenicity, the two persistent symptom clusters, causal attribution and interference with daily activities; and the lower band shows the evidence gap each element addresses. Arrows denote the a priori ordering tested, not established causal effects; alternative orderings were examined as robustness analyses (Supplementary Table S15).

Setting, participants and sampling

Data were collected in Tangail District, Dhaka Division, Bangladesh, between 17 May and 20 August 2026. The national campaign began in early 2021; every dose preceded the interview; dates of individual doses were not recorded, so the interval between vaccination and interview could not be calculated for each participant, but it could exceed five years. The 450 participants were selected by purposive sampling to secure representation across age groups, sexes, rural and urban residence, and occupational and health backgrounds, not to achieve probability

representation of the population. Eligibility required at least one documented dose and the capacity to give informed consent, with additional consent from a parent or guardian for participants younger than 18 years. Vaccination was confirmed against the participant's vaccination card or national digital certificate when available; otherwise the participant's report was accepted. Recruitment continued until each stratum quota was filled. The numbers of people approached, found ineligible, or declining were not recorded, so a response rate could not be calculated. Complete data were obtained for all 450 participants on every modelled variable. Details are given in Supplementary Methods S1.

Study size

The model contains 61 free parameters (7.4 cases per parameter). Rather than rely on case-to-parameter heuristics, power was evaluated in the root mean square error of approximation (RMSEA) framework:[39] for the test of close fit ($\varepsilon_0 = 0.05$) against $\varepsilon_1 = 0.08$ at $\alpha = 0.05$, power at N = 450 was > 0.999 for the structural model (159 degrees of freedom) and 0.991 for the measurement model (51 degrees of freedom) (Supplementary Methods S1).

Instrument and measures

A structured, interviewer-administered questionnaire was prepared for this study. Symptom items were adapted from the solicited-event lists used in the pivotal COVID-19 vaccine trials[2,3] and from a Bangladeshi post-vaccination survey,[12] and two appraisal items, on causal attribution and interference with daily activities, were written for this study. Before data collection, the questionnaire was pretested among non-participants equivalent to at least 5% of the sample size (≥23 people), who were not included in the main study, and the necessary adjustments were made to the questionnaire. Trained interviewers then administered the final questionnaire verbally in Bangla and kept item order and wording constant across interviews. The instrument was not formally validated or back-translated, and no formal cognitive

interviews were conducted; the implications are considered in the Discussion. It covered sociodemographic characteristics; medical history and lifestyle, including pre-existing conditions and previous SARS-CoV-2 infection; type and number of doses; symptoms within seven days of each dose; and new health problems lasting more than one month. Persistence was defined as any new problem since vaccination that had lasted more than one month, whether or not it had resolved by the interview. A screening question ("Since vaccination, have you experienced any new health problem that has lasted for more than one month?") was followed by the full checklist, which was administered to everyone rather than only to those answering yes. Causal attribution was the strength of agreement, on a five-point scale, that the symptoms experienced were due to vaccination (ATTRIB). Interference with daily activities (INTERF) was coded yes if participants reported that their symptoms interfered with daily activities. Both appraisal items were asked of all participants after the symptom modules, without a filter question. The items analysed are reproduced in the Supplementary Information (Appendix D).

Case ascertainment and its limits

All outcomes are self-reported symptoms recorded as present or absent. They were not graded for severity or seriousness, mapped to Brighton Collaboration case definitions of adverse events following immunisation (AEFI)[27,] or verified clinically. The figures are therefore prevalences of self-reported symptoms among vaccinated people, not incidences of vaccine-associated adverse events, and cannot be compared with an unvaccinated population.

Denominators for descriptive estimates

Each dose-specific proportion was calculated over the participants who received that dose (450, 407 and 216 for doses one to three), because using N = 450 would treat non-recipients as

symptom-free. Both denominators are given in Supplementary Table S11. Proportions are presented with 95% Wilson score intervals.

Symptom selection and cluster specification

Three latent constructs were specified a priori on the basis of symptom timing and plausibility. Acute reactogenicity (REACT) comprised five solicited events within seven days of the first dose: injection-site pain or swelling, fever, headache, muscle or joint pain and cold-like symptoms. The first dose was used because it was the only exposure shared by all participants. The persistent somatic-cognitive cluster (SOMCOG) comprised constant fatigue; migraine, dizziness, or brain fog; sleeping difficulty; and joint or muscle pain. This label was preferred to "neuro-psychological" because the cluster contains no mood or anxiety items. The persistent allergic-type cluster (ALLERG) comprised skin rash or itching, self-described allergy, and new food or medication allergy; the label describes self-reported content and implies no immunological mechanism.

Persistent indicators were retained if their prevalence exceeded 15% and they could be assigned a priori to one construct. This rule was adopted because rarer binary items produce sparse bivariate tables that destabilise polychoric estimation;[40] it does not imply that rarer symptoms are unimportant, and all excluded items are reported descriptively (Supplementary Tables S11 and S12). Menstrual cycle changes, applicable only to women, were reserved for a female-only model. Acute fatigue was excluded from REACT because 236 of the 238 participants reporting it (99.2%) also reported at least one retained indicator, so it marked whether a reaction occurred rather than its intensity. A prospective rule excluded an indicator only if its standardised loading had a standard error above 0.10, the solution was inadmissible, or more than 95% of endorsers also endorsed another indicator of the same construct; persistent fatigue met none of these criteria and was retained (Supplementary Methods S2).

Statistical analysis

A measurement model was estimated by confirmatory factor analysis, and the structural paths were then added, following the two-step approach.[41,42] All symptom indicators were binary, attribution had five ordered categories, and interference was binary; all were modelled as ordered categorical variables with a probit link and delta parameterisation, using robust weighted least squares with mean and variance adjustment (WLSMV), which is appropriate for categorical indicators.[40,43] Coefficients are standardised; for the categorical appraisal variables they refer to the underlying latent response, so R^2 values for ATTRIB and INTERF are not comparable with linear-regression R^2 values. Model equations, identification and degrees of freedom are given in Supplementary Methods S3 and S7.

The structural model regressed REACT on age band, sex, educational attainment, vaccine type (Pfizer-BioNTech and Moderna versus other or unspecified vaccines), number of doses, pre-existing health conditions, and marital status. SOMCOG and ALLERG were regressed on REACT and the same covariates, with their residuals allowed to correlate. ATTRIB was regressed on both persistent clusters, and INTERF on ATTRIB and both clusters. The indirect associations of each cluster with INTERF through ATTRIB were defined as products of coefficients, and the proportion of each total association accounted for by attribution was calculated as the indirect divided by the total association. Because each appraisal construct was a single item, no correction for measurement error was possible. Smoking, previous infection, residence and anthropometric variables were not included as covariates.

Composite reliability (coefficient omega), average variance extracted (AVE), the Fornell–Larcker criterion[44] and the heterotrait-monotrait ratio[45] were used to evaluate the measurement model. Fit was assessed with the scaled chi-square statistic, comparative fit index (CFI), Tucker-Lewis index (TLI), RMSEA and standardised root mean square residual (SRMR); CFI and TLI > 0.90 and RMSEA and SRMR < 0.08 were taken as adequate.[42] Because these cut-

offs were derived for maximum likelihood with continuous data and WLSMV tends to yield lower RMSEA and higher CFI for the same misspecification,[46,47] values close to the cut-offs were interpreted conservatively, and local misfit was examined with modification indices. Standard errors of indirect associations were obtained by the delta method and confirmed with Monte Carlo intervals based on 20,000 draws;[48] bootstrapping was not available because the covariates were treated as fixed. Differences between standardised coefficients were tested as defined parameters. The Benjamini-Hochberg procedure controlled the false discovery rate across the 24 covariate coefficients.[49] Two-sided $P < 0.05$ was considered statistically significant.

Robustness analyses

Eight sets of robustness analyses were prespecified in response to the design's limitations (Supplementary Methods S4 and S8). (i) Persistent fatigue was removed from SOMCOG. (ii) The model was refitted in women with menstrual cycle changes added to ALLERG. (iii) Because muscle or joint pain appeared in both REACT and SOMCOG, its two reports were allowed a residual correlation, and in a second model the item was removed from both constructs. (iv) Cold-like symptoms, the weakest acute indicator, were removed. (v) Because the appraisal items were posed to everyone, the model was refitted among participants reporting any acute or persistent symptom (n = 402) and among those reporting at least one modelled persistent symptom (n = 336). (vi) Common-method variance was examined with a single-factor model,[50] an unmeasured latent method factor with equal loadings on all symptom indicators,[50] and a marker variable, self-reported height category, which was measured in the same interview and is theoretically unrelated to vaccine symptoms.[51] (vii) Three alternative orderings were fitted: interference preceding attribution; attribution preceding the persistent clusters; and attribution preceding all symptom reports. Because equivalent and near-equivalent models cannot be distinguished by fit,[52] these comparisons were used to judge

whether the data favoured the hypothesised direction, not to establish causality. (viii) Observed proportions were tabulated to express associations as probabilities.

Software and data management

Data were prepared in Stata 17 and analysed in R 4.4.3 with lavaan 0.6-21[53], semTools 0.5-9, dplyr 1.2.1 and haven 2.5.4. Robustness analyses were run in R 4.3.3 with the same lavaan and semTools versions and reproduced the primary estimates exactly. Model syntax is provided in Supplementary Methods S5.

Results

Participant characteristics

All 450 participants had complete data on every modelled variable. Women made up 69.1% of the sample, 52.7% were aged 18-28 years and 21 (4.7%) were younger than 18 years; 54.9% held an honours degree or higher, 47.3% lived in urban areas, and 49.8% were married (Table 1; Supplementary Table S1). In the 2022 census, 51.8% of Tangail District residents were female, 22.6% lived in urban areas, 93.2% were Muslim, and 18.6% of those aged 10 years or older were aged 20–29 years;[54] the sample was therefore younger, more female, more urban and, judging by its educational attainment, more educated than the district population, and its percentages are not population estimates. All participants had received at least one dose, 407 at least two and 216 three. Pfizer-BioNTech was the most frequent product (39.6%), followed by other or unspecified vaccines (39.1%) and Moderna (21.3%); 15.8% reported a pre-existing condition and 6.4% previous SARS-CoV-2 infection.

Table 1. Sociodemographic, vaccination and medical characteristics of participants (N = 450).

Variable	Category	n (%)
Age	Below 18 years	21 (4.7)
	18-28 years	237 (52.7)
	29-39 years	108 (24.0)
	40-50 years	37 (8.2)
	More than 50 years	47 (10.4)
Sex	Male	139 (30.9)
	Female	311 (69.1)
Area of residence	Rural	237 (52.7)
	Urban	213 (47.3)
Marital status	Married	224 (49.8)
	Unmarried	226 (50.2)
Educational attainment	Primary or less	55 (12.2)
	Secondary (SSC)	82 (18.2)
	Higher secondary (HSC)	66 (14.7)
	Honours degree or above	247 (54.9)
SARS-CoV-2 infection before vaccination[a]	Yes	29 (6.4)
	No	421 (93.6)
COVID-19 vaccine received[b]	Pfizer-BioNTech	178 (39.6)
	Moderna	96 (21.3)
	Other or unspecified vaccines (reference)	176 (39.1)
Vaccine doses received	One dose	43 (9.6)
	Two doses	191 (42.4)
	Three doses	216 (48.0)
Smoking	Yes	16 (3.6)
	No	434 (96.4)
Pre-existing health condition	Yes	71 (15.8)
	No	379 (84.2)

Values are n (%). SSC, Secondary School Certificate; HSC, Higher Secondary Certificate. That 237 participants were aged 18-28 years and 237 lived in rural areas is a coincidence verified against the raw data. [a]Self-reported and not serologically confirmed. [b]The reference category comprises Oxford-AstraZeneca (n = 33), Sinovac (n = 6) and other or unspecified products (n = 137), a heterogeneous comparison group. Anthropometric measures, religion, occupation and comorbidity subcategories are reported in Supplementary Table S1.

Prevalence of acute and persistent symptoms

At least one symptom within seven days was reported by 75.8% [71.6, 79.5] of first-dose, 73.7% [69.2, 77.8] of second-dose and 80.6% [74.8, 85.3] of third-dose recipients, led by injection-site pain or swelling and fever (Table 2). Calculated over the recipients of each dose, reactogenicity did not decline across doses; calculated over the full sample, it would appear to fall from 75.8% to 66.7% and 38.7%, an arithmetic consequence of fewer recipients (Supplementary Table S11).

Table 2. Self-reported symptoms within seven days of each COVID-19 vaccine dose, computed over the participants who received that dose.

Symptom	Dose 1 (n = 450)	Dose 2 (n = 407)	Dose 3 (n = 216)
Any symptom within 7 days	341 (75.8) [71.6, 79.5]	300 (73.7) [69.2, 77.8]	174 (80.6) [74.8, 85.3]
Pain or swelling at injection site[a]	288 (64.0) [59.5, 68.3]	264 (64.9) [60.1, 69.3]	148 (68.5) [62.0, 74.3]
Fever[a]	258 (57.3) [52.7, 61.8]	235 (57.7) [52.9, 62.4]	141 (65.3) [58.7, 71.3]
Fatigue[b]	238 (52.9) [48.3, 57.5]	204 (50.1) [45.3, 55.0]	114 (52.8) [46.1, 59.3]
Headache[a]	155 (34.4) [30.2, 38.9]	128 (31.4) [27.1, 36.1]	94 (43.5) [37.1, 50.2]
Muscle or joint pain[a]	142 (31.6) [27.4, 36.0]	121 (29.7) [25.5, 34.3]	73 (33.8) [27.8, 40.3]
Sleeping problems	100 (22.2) [18.6, 26.3]	83 (20.4) [16.8, 24.6]	55 (25.5) [20.1, 31.7]
Cold-like symptoms[a]	81 (18.0) [14.7, 21.8]	66 (16.2) [13.0, 20.1]	32 (14.8) [10.7, 20.2]

Values are n (%) with 95% Wilson score intervals. Symptoms were recorded as present or absent, were not graded and were not mapped to standardised case definitions. Seven less frequent symptoms (nausea or vomiting, stomach pain, chest pain, persistent cough, increased heart rate, raised blood pressure and diarrhoea; each ≤ 13.0% after any dose) are reported in Supplementary Table S11. [a]Indicator of acute reactogenicity (first-dose responses only). [b]Not entered because 236 of 238 first-dose reporters (99.2%) also reported a retained indicator; that 238 participants also agreed that their symptoms were due to vaccination (Table 3) is a verified coincidence.

Overall, 72.0% [67.7, 75.9] answered yes to the screening question on a new problem lasting more than one month, and the prevalence of the seven modelled persistent symptoms ranged from 37.6% to 55.3% (Table 3). Because the checklist was asked of everyone, the two measures did not coincide exactly: 336 participants endorsed at least one modelled item, including 13 who had answered no to the screening question, whereas 1 participant answered yes but endorsed no modelled item. Just over half agreed or strongly agreed that their symptoms were due to vaccination (52.9%), and 51.8% reported interference with daily activities. Self-reported chronic conditions were uncommon (≤ 7.3%) and could not be classified reliably as new; for example, 20 of the 51 participants reporting persistent asthma symptoms had reported asthma before vaccination (Supplementary Table S12).

Table 3. Problems lasting more than one month after COVID-19 vaccination, causal attribution and interference with daily activities (N = 450).

Variable	Category	n (%) [95% CI]
Any new problem lasting more than one month (screening question)	Yes	324 (72.0) [67.7, 75.9]
Constant fatigue[a]	Yes	249 (55.3) [50.7, 59.9]
Migraine, dizziness or brain fog[a]	Yes	219 (48.7) [44.1, 53.3]
Joint or muscle pain[a]	Yes	206 (45.8) [41.2, 50.4]
Sleeping difficulty[a]	Yes	169 (37.6) [33.2, 42.1]
Skin rash or itching[b]	Yes	221 (49.1) [44.5, 53.7]
Allergy[b,c]	Yes	205 (45.6) [41.0, 50.2]
New food or medication allergy[b,c]	Yes	179 (39.8) [35.4, 44.4]

Variable	Category	n (%) [95% CI]
Causal attribution: symptoms believed to be due to vaccination	Strongly agree	180 (40.0) [35.6, 44.6]
	Agree	58 (12.9) [10.1, 16.3]
	Neutral	105 (23.3) [19.7, 27.5]
	Disagree	72 (16.0) [12.9, 19.7]
	Strongly disagree	35 (7.8) [5.6, 10.6]
Interference with daily activities	Yes	233 (51.8) [47.2, 56.4]
	No	217 (48.2) [43.6, 52.8]

Values are n (%) with 95% Wilson score intervals. Persistence means any new problem since vaccination that lasted more than one month, whether or not it had resolved by the interview; recall could exceed five years. No item was clinically verified, and no unvaccinated comparison group was available, so these figures are not estimates of vaccine-attributable risk. [a]Indicator of the persistent somatic–cognitive cluster. [b]Indicator of the persistent allergic-type cluster. [c]Lay term, not clinically or serologically confirmed. Menstrual cycle changes, chest pain or increased heart rate, asthma symptoms and self-reported chronic conditions are reported in Supplementary Table S12.

Measurement model

Fit of the three-factor measurement model was mixed: the incremental indices were acceptable (CFI = 0.961, TLI = 0.949), but RMSEA (0.088, 90% CI [0.076, 0.099]) and SRMR (0.094) exceeded 0.08, and $\chi^2(51) = 226.64$ ($P < 0.001$; $\chi^2/df = 4.44$). Because WLSMV tends to understate RMSEA, this value indicated appreciable misfit.[47] The largest modification indices concerned the allergic-type items (a cross-loading of new food or medication allergy on SOMCOG and a residual correlation between rash and allergy), indicating that these items are not cleanly separated. All loadings were significant and all except cold-like symptoms (0.381) were 0.666 or higher (Table 4). Two clusters were dominated by one item (constant fatigue, 0.971; skin rash or itching, 0.964), so each represented a principal complaint with related symptoms. Composite reliability ranged from 0.712 to 0.857, and the AVE exceeded 0.50 for each construct. The constructs were moderately to strongly correlated (0.528-0.663); the Fornell–Larcker and heterotrait–monotrait criteria were met, so the clusters were correlated but statistically distinct rather than independent (Supplementary Tables S2–S5).

A single-factor model fitted substantially worse (CFI = 0.899, RMSEA = 0.137, SRMR = 0.145).

Table 4. Measurement model: standardised loadings, reliability and validity (N = 450).

Construct	Indicator	λ	SE	95% CI	ω	AVE	√AVE
Acute reactogenicity	Injection-site pain or swelling	0.709	0.056	[0.600, 0.818]	0.712	0.511	0.715
	Fever	0.702	0.052	[0.600, 0.805]			
	Headache	0.852	0.042	[0.770, 0.935]			
	Muscle or joint pain	0.829	0.045	[0.741, 0.917]			
	Cold-like symptoms	0.381	0.068	[0.247, 0.515]			
Persistent somatic–cognitive	Constant fatigue	0.971	0.017	[0.937, 1.005]	0.849	0.761	0.872
	Migraine, dizziness or brain fog	0.906	0.021	[0.865, 0.948]			
	Sleeping difficulty	0.666	0.043	[0.581, 0.751]			
	Joint or muscle pain	0.915	0.019	[0.877, 0.953]			
Persistent allergic-type	Skin rash or itching	0.964	0.030	[0.905, 1.023]	0.857	0.754	0.868
	Allergy	0.844	0.034	[0.777, 0.911]			
	New food or medication allergy	0.787	0.045	[0.699, 0.876]			

All loadings $P < 0.001$. Model fit: $\chi^2(51) = 226.64$, $\chi^2/df = 4.44$, CFI = 0.961, TLI = 0.949, RMSEA = 0.088 [0.076, 0.099], SRMR = 0.094. Inter-factor correlations: REACT-SOMCOG 0.645, REACT-ALLERG 0.528, SOMCOG-ALLERG 0.663; heterotrait–monotrait ratios 0.616, 0.544 and 0.707. λ, standardised loading; SE, standard error; CI, confidence interval; ω, coefficient omega; AVE, average variance extracted. Upper bounds above 1.0 arise from symmetric Wald intervals on a parameter bounded at unity; residual variances remained positive.

Structural model

The structural model fitted acceptably on CFI, TLI and RMSEA ($\chi^2(159) = 419.79$, $P < 0.001$, CFI = 0.953, TLI = 0.973, RMSEA = 0.060 [0.053, 0.068]), whereas SRMR (0.087) was marginally above 0.08 (Table 5; Fig. 2). The covariates together explained 8.0% of the variance in acute reactogenicity; higher education was associated with fewer acute symptoms, and Moderna (relative to other or unspecified vaccines) and pre-existing conditions with more. All six nominally significant covariate coefficients remained significant after false-discovery-rate adjustment (largest q = 0.036; Supplementary Table S6).

Stronger acute reactogenicity was associated with greater persistent burden in both the somatic–cognitive (β = 0.624, 95% CI [0.535, 0.712]) and allergic-type (β = 0.558 [0.451,

0.664]) clusters. In observed terms, 94.6% (176/186) of participants reporting three to five acute reactions reported a persistent symptom, compared with 51.4% (54/105) of those reporting none (Supplementary Table S16). The two clusters remained correlated after accounting for acute reactogenicity (residual r = 0.45 [0.31, 0.59]), consistent with a general tendency to report persistent symptoms. Older age and lower education were associated with greater somatic–cognitive burden, and more doses with greater allergic-type burden.

Both clusters were associated with stronger attribution (somatic–cognitive β = 0.331; allergic-type β = 0.524; both $P < 0.001$), and attribution was associated with interference (β = 0.497 [0.328, 0.666]), alongside direct associations of the somatic–cognitive (β = 0.229) and allergic-type (β = 0.321) clusters. The attribution coefficient was larger than the direct somatic–cognitive coefficient (difference 0.268 [0.005, 0.532], $P = 0.046$) but did not differ significantly from the direct allergic-type coefficient (difference 0.176 [−0.117, 0.469], $P = 0.24$), and it was smaller than the total association of the allergic-type cluster with interference (0.582). Attribution was therefore one of several comparably strong correlates of interference, not demonstrably the strongest. Observed proportions showed the same gradient: interference was reported by 0% (0/35) and 2.8% (2/72) of those who strongly disagreed or disagreed that their symptoms were due to vaccination, 21.9% (23/105) of neutral participants, and 94.8% (55/58) and 85.0% (153/180) of those who agreed or strongly agreed (Supplementary Table S16).

Table 5. Standardised path coefficients of the structural model (N = 450).

Outcome	Predictor	β	SE	95% CI	*P*
Acute reactogenicity ($R^2 = 0.080$)	Age band	-0.002	0.077	[−0.153, 0.148]	0.978
	Female	0.076	0.061	[-0.044, 0.196]	0.217
	Education	-0.192	0.061	[-0.312, -0.072]	0.002
	Moderna	0.159	0.060	[0.042, 0.277]	0.008
	Pfizer	0.078	0.063	[-0.046, 0.203]	0.217
	Doses received	-0.009	0.059	[-0.124, 0.105]	0.874

Outcome	Predictor	β	SE	95% CI	*P*
	Comorbidity	0.138	0.053	[0.035, 0.241]	0.009
	Married	-0.033	0.071	[-0.172, 0.105]	0.636
Persistent somatic–cognitive (R^2 = 0.640)	Acute reactogenicity	0.624	0.045	[0.535, 0.712]	< 0.001
	Age band	0.293	0.062	[0.171, 0.415]	< 0.001
	Education	-0.177	0.044	[-0.264, -0.091]	< 0.001
	Comorbidity	-0.083	0.048	[-0.178, 0.012]	0.085
Persistent allergic-type (R^2 = 0.381)	Acute reactogenicity	0.558	0.054	[0.451, 0.664]	< 0.001
	Doses received	0.143	0.048	[0.048, 0.238]	0.003
	Female	0.092	0.053	[-0.011, 0.196]	0.080
Causal attribution (R^2 = 0.604)	Persistent somatic-cognitive	0.331	0.073	[0.187, 0.475]	< 0.001
	Persistent allergic-type	0.524	0.070	[0.387, 0.661]	< 0.001
Interference with daily activities (R^2 = 0.881)	Causal attribution	0.497	0.086	[0.328, 0.666]	< 0.001
	Persistent somatic-cognitive	0.229	0.071	[0.089, 0.369]	0.001
	Persistent allergic-type	0.321	0.080	[0.163, 0.479]	< 0.001

Coefficients describe associations in a cross-sectional model, not causal effects. Covariates with $P \geq 0.10$ are omitted from the persistent-cluster equations; all 24 covariate paths with Benjamini–Hochberg q values are in Supplementary Table S6. Residual correlation between the persistent clusters r = 0.45 [0.31, 0.59]. R^2 values for attribution and interference refer to latent responses of single ordered-categorical items and are not comparable with linear-regression R^2. Model fit: $\chi^2(159) = 419.79$, $\chi^2/df = 2.64$, CFI = 0.953, TLI = 0.973, RMSEA = 0.060 [0.053, 0.068], SRMR = 0.087; TLI exceeds CFI because the baseline model conditions on fixed covariates (Supplementary Methods S3). β, standardised coefficient; SE, standard error; CI, confidence interval.

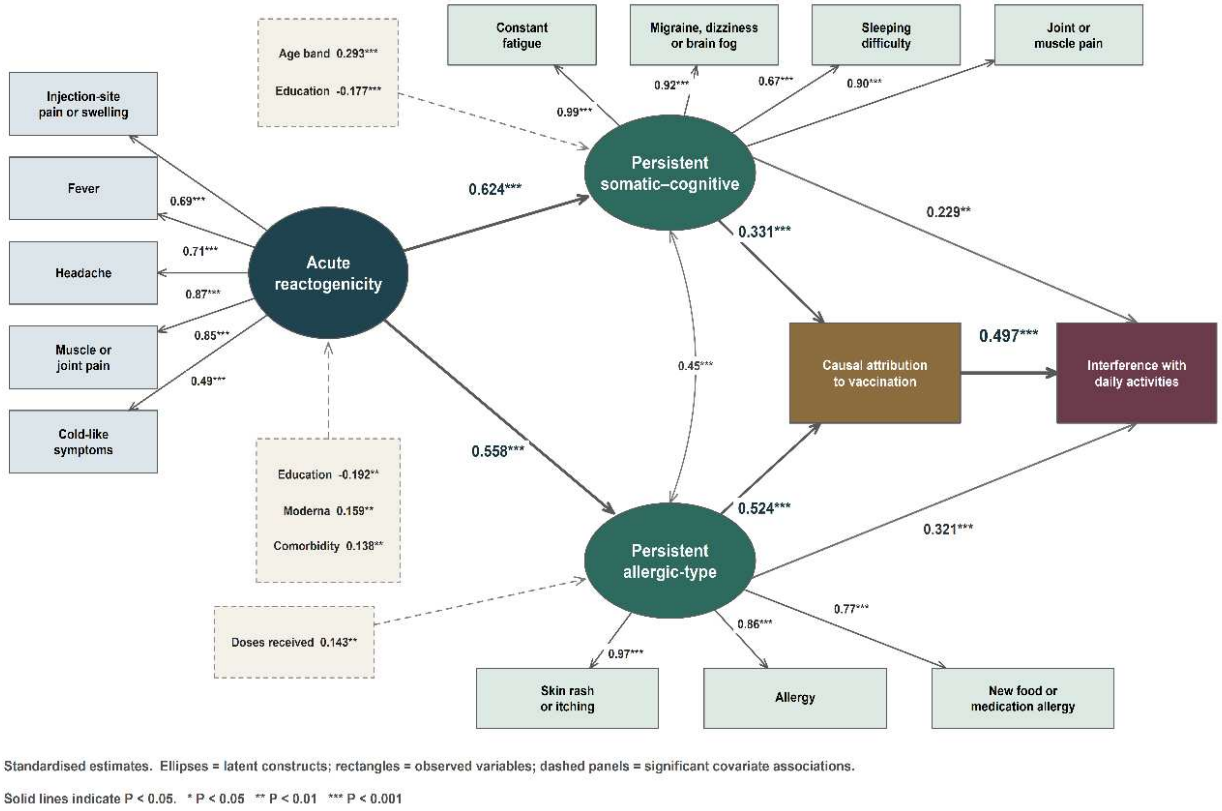


Figure 2: Structural equation model of acute reactogenicity, persistent symptom clusters, causal attribution and interference with daily activities after COVID-19 vaccination (N = 450). Standardised estimates from a cross-sectional model; arrows show the hypothesised ordering, and alternative orderings fitted comparably (Supplementary Table S15). Ellipses represent latent constructs, rectangles observed variables and dashed panels statistically significant covariate associations. A residual covariance between the two persistent clusters was freely estimated (r = 0.45, $P < 0.001$). Indicator loadings are those estimated in the full structural model and therefore differ slightly from the measurement-model loadings in Table 4. Non-significant covariate paths are omitted. $^{**}P < 0.01$, $^{***}P < 0.001$.

Indirect associations through attribution

The indirect association through attribution was 0.164 (95% CI [0.073, 0.256]) for the somatic-cognitive cluster and 0.260 [0.166, 0.355] for the allergic-type cluster, against total associations of 0.393 [0.248, 0.538] and 0.582 [0.441, 0.722]. Attribution therefore statistically accounted for 41.8% (Monte Carlo 95% CI 22.0-69.4%) and 44.8% (28.4-66.0%) of the respective associations with interference; the direct associations remained significant (Supplementary

Table S7). These were decompositions of cross-sectional associations and did not establish mediation.

Robustness analyses

The principal associations were stable across specifications (Supplementary Tables S8-S10 and S13-S15). Removing persistent fatigue, restricting to women, removing cold-like symptoms or adding the height marker as a covariate changed the key coefficients by small amounts, and all remained significant. The two reports of muscle or joint pain shared a residual correlation (r = 0.456 [0.093, 0.819]; $\Delta\chi^2(1) = 6.08$, $P = 0.014$), but allowing for it changed the acute-to-persistent coefficients only from 0.624 and 0.558 to 0.609 and 0.561; with the item removed from both constructs they were 0.580 and 0.512.

Among participants reporting any symptom (n = 402), all hypothesised paths remained significant (acute to persistent β = 0.524 and 0.428; attribution to interference β = 0.518), although fit was weaker (CFI = 0.914, SRMR = 0.107). Among those reporting at least one persistent symptom (n = 336), attribution remained associated with interference (β = 0.537) and both clusters with attribution (β = 0.277 and 0.489); the acute-to-allergic coefficient fell to 0.260, as expected when the sample is selected on persistent symptoms, and fit was poor (CFI = 0.849, SRMR = 0.114). Interference was reported by 4.7% of symptomatic participants who disagreed or strongly disagreed that their symptoms were due to vaccination and by 86.3% of those who strongly agreed.

An equal-loading method factor accounted for about 17% of each symptom indicator's variance (standardised loading 0.409) without significantly improving fit ($\Delta\chi^2(1) = 1.54$, $P = 0.21$) and reduced the inter-cluster correlations to 0.37-0.57; it could not be estimated in the full structural model. The height marker correlated between -0.256 and 0.055 with the substantive items (smallest absolute value 0.003), implying a negligible Lindell-Whitney

adjustment.[51] These checks argued against a single dominant method factor but could not exclude correlated reporting tendencies.

Alternative orderings fitted as well as the hypothesised model (Supplementary Table S15). Reversing the final link, so that interference preceded attribution, produced an equivalent model with identical fit. Placing attribution before the persistent clusters fitted slightly better (CFI = 0.958, RMSEA = 0.057, SRMR = 0.084), as did placing it before all symptom reports. The data therefore did not favour the hypothesised direction over the alternatives.

Discussion

In this retrospective study, post-vaccination symptoms grouped into three clusters that were correlated with one another but statistically distinct: acute reactogenicity, a persistent somatic–cognitive cluster and a persistent allergic-type cluster. Stronger first-week reactions were associated with a greater persistent symptom burden, whereas participant characteristics explained little of the variation in acute reactions. Stronger attribution of symptoms to vaccination was associated with interference with daily activities and accounted statistically for 42–45% of each cluster's association with interference. The direction of these associations could not be established, as alternative orderings fitted the data equally well.

The acute prevalences exceeded those recorded by passive surveillance and by a national online survey in Bangladesh (39.5% overall, but about 80% after Pfizer-BioNTech or Moderna),[12] consistent with the predominance of mRNA products here and with the higher yield of solicited checklists. They lay within the range reported by trials and pooled analyses[2,3,15,22] and by a UK community cohort.[20] Reactogenicity did not decline across doses, unlike the trend reported among Bangladeshi medical students;[13] because third-dose recipients were self-selected, the third dose was the most recent, and booster products often differed, this finding was not evidence of a dose–response relationship. Self-reported chronic conditions were uncommon;

however, without a comparison group or clinical verification, these data cannot speak to the frequency of serious adverse events.

The measurement results supported modelling co-occurring symptoms as clusters,[33] an approach that has been informative in oncology and chronic respiratory disease[34,36] and could complement symptom-by-symptom vaccine safety analysis by retaining the covariance among complaints. Three qualifications apply. First, the three constructs were moderately to strongly correlated (r = 0.53–0.66), and the measurement model showed appreciable misfit, concentrated among the allergic-type items. Discriminant validity was nevertheless supported by the Fornell–Larcker and heterotrait–monotrait criteria,[44,45] so the clusters are better described as correlated dimensions of one symptom experience than as the relatively independent groups envisaged in the original definition of a symptom cluster.[33] Second, two clusters were dominated by a single complaint, fatigue or rash. Third, convergent validity of the acute construct was only marginal (AVE 0.511). Because the AVE is the mean of the squared standardised loadings, this value reflected the low loading of cold-like symptoms (0.381; squared loading 0.145), against a mean squared loading of 0.602 for the other four acute indicators. Cold-like complaints may partly reflect intercurrent respiratory infection, which occurs in the weeks after vaccination,[20] rather than reactogenicity, although this could not be verified; removing the item left the principal coefficients essentially unchanged (Supplementary Table S13). The allergic-type label describes self-reported content only, and the loading of menstrual changes among women reflected covariance, not an allergic mechanism.

Three explanations are compatible with the association between acute and persistent symptoms, and the present design could not separate them. The first is biological. In a Korean study, Heo et al. found that the pro-inflammatory response to a first dose of the adenoviral-vector vaccine ChAdOx1 nCoV-19 was associated with systemic reactions,[18] and Hervé et al.

described reactogenicity as the clinical expression of an inflammatory response modulated by host factors.[17] A strong early innate response might therefore mark people who are prone to longer-lasting symptoms. The second explanation concerns reporting style. Some individuals perceive bodily sensations as more intense and report them more readily, a tendency described as somatosensory amplification.[55] In a Danish national cohort, Hansen et al. found that health anxiety and vaccine concern predicted self-reported adverse events after COVID-19 vaccination,[30] and a meta-analysis of placebo arms showed that systemic complaints were frequent even without an active vaccine.[28] Such a tendency would raise reports at both time points and is consistent with the residual correlation between the two persistent clusters (r = 0.45). The third explanation is recall bias. Participants who currently experience, or attribute, persistent symptoms may remember their first-week reactions as more intense. Recall bias is more likely when recall is generally poor,[56] as it tends to be after long intervals, and here the interval could exceed five years, so this bias cannot be excluded. Part of the association may also reflect shared symptom content, as muscle or joint pain contributed to both constructs, although removing the item changed the coefficients little (0.580 and 0.512; Supplementary Table S13).

The association of attribution with interference was consistent with the common-sense model, in which the perceived cause of a sensation shapes the response to it,[37,38] and with nocebo evidence from vaccine trials.[28,29] That evidence, however, showed that expectations can precede and generate symptoms, which is the reverse of the ordering modelled here; health anxiety, vaccine concern and hesitancy also predicted symptom reports.[30,31] In the present data, alternative models fitted at least as well when attribution preceded symptom reports, and reversing the final link produced an equivalent model.[52] The relationship may therefore run in both directions. Interference with daily activities may lead people to search for a cause and to attribute their symptoms to vaccination, whereas attribution may heighten attention to

symptoms and amplify their reported impact; the common-sense model treats illness representations and their consequences as dynamically linked in this way.[37] Anxiety, trust in health authorities and vaccine hesitancy, which are associated with vaccine acceptance[6] and with the reporting of adverse events[30,31] and could therefore influence both causal beliefs and symptom reports, were not measured. Attribution should therefore be regarded as a correlate of interference that merits prospective investigation, not as an established target for intervention.

The associations with education and age warrant brief comment. Lower education was associated with more acute and persistent symptoms, as in a national Bangladeshi survey[12] but opposite to the gradient reported in Quebec,[31] which suggests that reporting may depend on context. Older age was associated with a greater persistent but not acute burden, although younger recipients are generally more reactogenic in the acute phase;[19] background morbidity may partly account for this (Supplementary Note S2).

Overall, headline figures such as 72.0% and 51.8% describe what participants in this sample recalled; they are not estimates of vaccine-caused harm and should not be quoted without that qualification. Presented out of context, such figures could be mistaken for risks attributable to vaccination and could reinforce vaccine hesitancy, which fear of side effects and misinformation are known to sustain.[7,8] The findings generate hypotheses for practice that require prospective testing (Fig. 3). Active surveillance systems, such as the US v-safe programme[57] and the UK COVID Symptom Study app,[20] have shown that first-week reactions can be recorded systematically at scale. Recording these reactions could help identify recipients who may need follow-up: in this sample, 94.6% of participants with three to five first-week reactions recalled at least one persistent symptom, compared with 51.4% of those with none (Supplementary Table S16). However, a rule of three or more reactions would flag 41.3% of recipients, so its yield and benefit must be evaluated before adoption. Adding symptom

duration to adverse-event reporting, coded to standardised case definitions,[27] would allow persistent presentations to be counted rather than recalled. Counselling that explains what to expect, without dismissing symptoms, is plausible given the attribution findings and evidence that pre-vaccination concern predicts reporting,[17,30] but it remains a hypothesis to be tested in trials; implying that symptoms are imagined would be inaccurate and could erode trust.[6,8] A primary-care pathway for prolonged complaints that considers alternative diagnoses, including undiagnosed prior infection, could be piloted in LMIC settings where referral pathways are limited.[11,14]

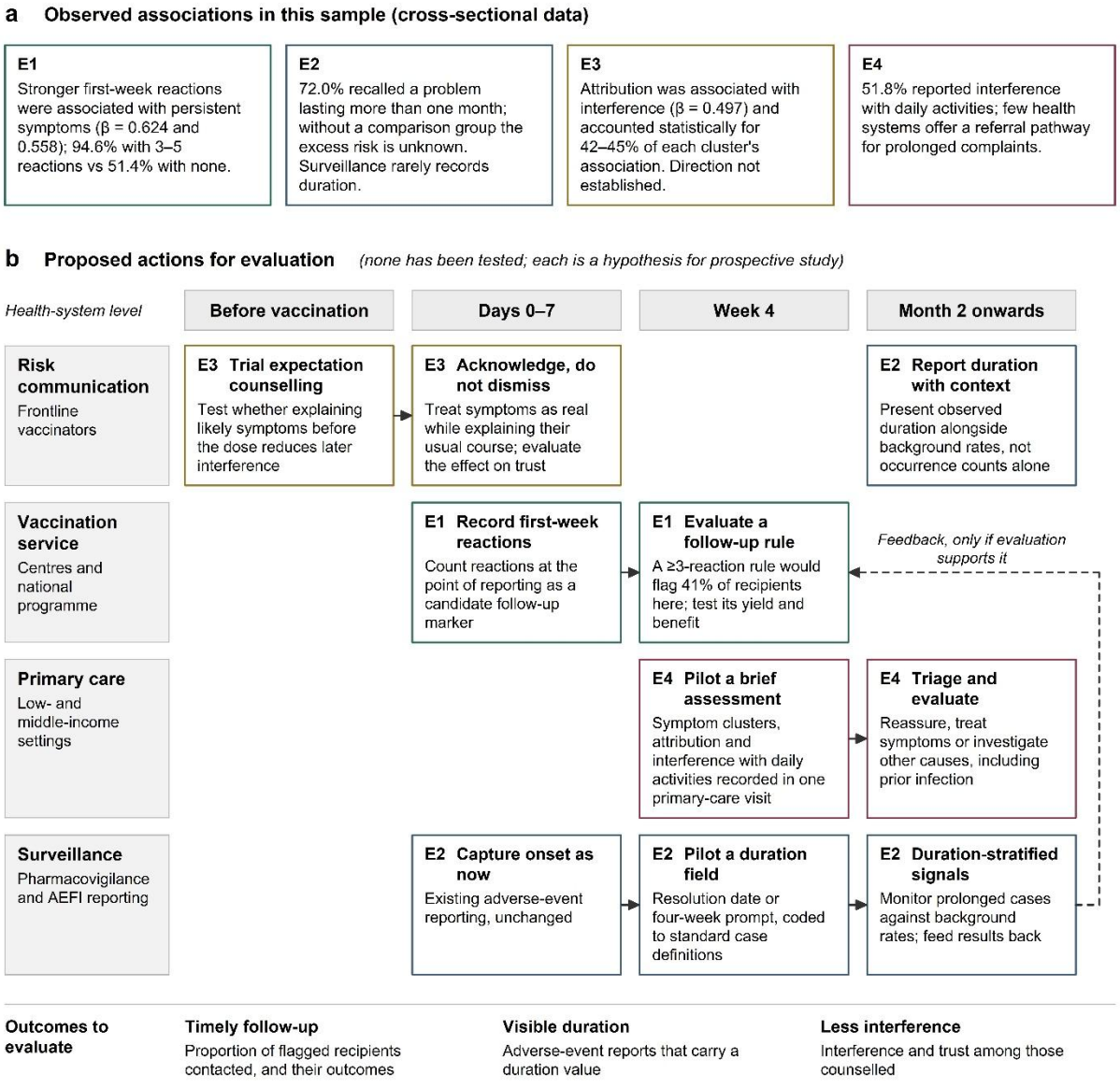


Figure 3 Proposed framework for evaluation: A hypothesis-generating framework derived from cross-sectional associations; none of the actions shown has been tested. Rows represent levels of the health system and columns represent timing relative to vaccination. Codes E1-E4 link each proposed action to the observed association that motivates it. Solid arrows indicate sequence within a level; the dashed loop indicates that duration data from surveillance could refine the follow-up rule if evaluation supports it.

Several limitations should be considered when interpreting these findings. They concern selection, information, confounding and modelling.

Selection: Participants were recruited purposively from one district and were younger, more often female, more urban and more educated than the district population.[54] The numbers of people approached and declining were not recorded, so non-response bias could not be assessed, and the percentages should not be read as population estimates.

Information: All data were self-reported and retrospective, and the interval between vaccination and interview could exceed five years, which increased the scope for recall error and differential recall.[56] "Lasting more than one month" referred to any period since vaccination. Symptoms were not graded, clinically verified or mapped to standardised case definitions.[27] The questionnaire was adapted for this study and, although it was pretested among non-participants, it was not formally validated or back-translated, and no formal cognitive interviews were conducted; its content validity, the equivalence of the Bangla wording with the source items and the reliability of recalled responses are therefore unknown, and participants may have interpreted some items differently.[58] Attribution and interference were each measured with a single unvalidated item, so their measurement error could not be modelled; this would tend to attenuate the attribution–interference coefficient and to overstate the direct associations of the clusters with interference. As the appraisal items were asked of everyone, associations in the full sample partly reflected the contrast between symptomatic and asymptomatic respondents, although they persisted among symptomatic participants.

Confounding: Without an unvaccinated comparison group, the 72.0% who reported persistent problems cannot be distinguished from the background prevalence of symptoms such as fatigue, itching and poor concentration, which are common in the general population. Prior infection was self-reported and probably under-ascertained,[21] so post-infectious symptoms that resemble long COVID[25,26] may have contributed. Anxiety, trust and hesitancy were not measured, and time since vaccination was not recorded, so it may have confounded the association between the number of doses and allergic-type burden.

Modelling: Model fit was mixed, with appreciable misfit in the measurement model. Common-method checks argued against a single method factor but could not exclude correlated reporting tendencies,[50] as the method factor could be estimated only in the measurement model and no purpose-designed marker item was included; self-reported height, which is associated with sex, served as an imperfect substitute.[51] The latent-response R^2 of 0.881 for interference is a property of a single-item model, not an estimate of explained real-world impairment. Coefficients of variables measured on different scales are not directly comparable, and alternative orderings fitted equally well, so the direction of the modelled associations remains unresolved.

These limitations indicate five ways in which future research could advance this work. First, the questionnaire should be developed into a validated instrument through forward and back translation, expert review and cognitive interviewing in Bangla,[58] followed by tests of test–retest reliability and of agreement with immunisation records or clinical notes. Such verification matters because the accuracy of self-report varies by vaccine: in a UK study, self-reported influenza vaccination agreed well with general-practice records, whereas self-reported pneumococcal vaccination had low sensitivity.[59] Reliability and validity should be assessed against consensus standards for measurement properties, such as the COSMIN checklist.[60] Second, attribution and interference should be measured with validated multi-item scales, such

as established illness-perception and functional-status measures, so that their measurement error can be modelled rather than ignored. Third, a marker item that is theoretically unrelated to vaccination but shares the response format of the substantive items should be built into the questionnaire at the design stage, allowing a formal adjustment for common-method variance.[50,51] Fourth, prospective cohorts that record dose dates and first-week reactions in diaries at the time of vaccination, and then assess persistent symptoms, attribution and interference with daily activities repeatedly, would establish temporal order and allow cross-lagged models to compare the competing directions directly. Fifth, an unvaccinated or delayed-vaccination comparison group, serological confirmation of prior infection[21] and baseline measures of anxiety, trust and vaccine hesitancy[30] would separate vaccine-related symptoms from background prevalence, post-infectious illness and reporting tendencies. Multi-district probability samples in Bangladesh and in other LMICs would then test whether the cluster structure and the attribution–interference association generalise, and randomised trials could evaluate whether pre-vaccination counselling reduces interference without lowering uptake or trust (Supplementary Note S2, C2.9).

Conclusion

Among 450 vaccinated people in Tangail District, Bangladesh, recalled post-vaccination symptoms formed three correlated clusters: acute reactogenicity, a persistent somatic-cognitive cluster, and a persistent allergic-type cluster. Stronger first-week reactions were associated with a greater persistent burden in both clusters, whereas sociodemographic and vaccine characteristics explained only 8.0% of the variance in acute reactions. Stronger attribution of symptoms to vaccination was associated with interference with daily activities and accounted statistically for 42-45% of each cluster's association with interference; these associations held among symptomatic participants. However, purposive sampling in one district, retrospective

self-report through a questionnaire that was not formally validated, single-item appraisal measures, the absence of an unvaccinated comparison group, and comparably fitting alternative orderings mean that neither the direction nor the causal meaning of these associations can be inferred. Prospective cohorts with validated instruments, recorded dose dates, baseline measures of anxiety and trust, and a comparison group are needed. Meanwhile, adding symptom duration to adverse-event reporting and testing respectful pre-vaccination counselling in trials are reasonable next steps for immunisation programmes.

Ethics approval and consent to participate

The study protocol was approved by the Ethical Review Committee of Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh (reference no. MBSTU/ERC/ECC/157/43), on 17 May 2026, before data collection began. The approved protocol included participants younger than 18 years with parental consent. All procedures followed the Declaration of Helsinki and relevant institutional guidelines and regulations. Written informed consent was obtained from all participants and, for those younger than 18 years, also from a parent or legal guardian, with the participant's assent recorded. Identifying information was removed before analysis (Supplementary Methods S6).

Use of generative AI and AI-assisted technologies

Generative AI tools were not used to generate data, and all analytic decisions and interpretations are the authors' own. After the first draft was completed, Grammarly was used for grammar checking, and Claude (Anthropic) was used to improve language clarity and sentence structure and to assist in drafting and debugging the R code used for model estimation and figure rendering. The authors ran and verified all code, checked every reported estimate against the software output, reviewed and edited all text, and take full responsibility for the accuracy, integrity, and originality of the published work.

Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request. Analysis code reproducing the primary specification and the robustness analyses is provided in Supplementary Methods S5 and S8.

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Author contributions (CRediT):

M.H.A.: Conceptualization; Methodology; Formal analysis; Investigation; Validation; Project administration; Resources; Visualization; Supervision; Writing - review & editing.

S.A.: Methodology; Investigation; Validation; Visualization; Writing - review & editing.

F.A.K.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

M.S.M.: Conceptualization; Methodology; Investigation; Data curation; Software; Validation; Formal analysis; Visualization; Project administration; Resources; Writing - review & editing (lead).

A.K.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

F.N.M.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

N.S.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

E.H.E.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

S.B.H.: Methodology; Formal analysis; Investigation; Validation; Visualization; Writing - review & editing.

M.H.H.: Conceptualization; Methodology; Formal analysis; Investigation; Validation; Visualization; Resources; Supervision; Writing - review & editing.

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Consent for publication

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Originality statement

The authors confirm that this manuscript is original, has not been published previously, and is not under consideration for publication elsewhere, in whole or in part.

Additional information

Supplementary information. The online version contains Supplementary Information organised as Appendices A-E: Appendix A, Supplementary Note S1 (extended background); Appendix B, Supplementary Methods S1-S8; Appendix C, Supplementary Tables S1-S16 and Supplementary Note S2; Appendix D, the survey instrument; and Appendix E, the completed STROBE checklist (Supplementary Table S17).

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