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Clinical Characteristics and Outcomes of Breakthrough Respiratory Vaccine-Preventable Infections in Adults and Children: A Multicentre Retrospective Case Series from Hyderabad, Telangana.

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Abstract

Background: Respiratory vaccine-preventable infections continue to occur in vaccinated individuals. Characterising these breakthrough episodes is important for identifying groups in whom vaccine-induced protection is attenuated and for informing booster and catch-up strategies in settings with heterogeneous immunisation coverage. ***Objective:*** To describe the demographic profile, clinical characteristics, and in-hospital outcomes of adults and children presenting with breakthrough respiratory vaccine-preventable infections at three hospitals in Nirmalpur, Sagara Pradesh, India, and to identify patient characteristics associated with severe disease. ***Methods:*** We conducted a multicentre retrospective case series at three hospitals between 1 January 2026 and 30 June 2026. Patients of any age with a laboratory-confirmed respiratory infection caused by a vaccine-preventable pathogen, and with documented age-appropriate vaccination against that pathogen completed at least 14 days before symptom onset, were eligible. Data were extracted from electronic and paper records using a standardised, pilot-tested proforma. The primary outcome was severe disease, defined as receipt of respiratory support beyond low-flow oxygen, admission to intensive care, receipt of vasopressors, or in-hospital death. Associations with the primary outcome were examined using multivariable logistic regression with robust standard errors clustered by hospital. ***Results:*** Of 412 patients screened, 314 were included (186 adults, 128 children). Median age was 34 years (IQR 6–58) and 149 (47.5%) were female. The most frequently identified pathogens were influenza A/B (112, 35.7%) and SARS-CoV-2 (96, 30.6%). Severe disease occurred in 71 patients (22.6%, 95% CI 18.2–27.5) and was more frequent in adults than children (30.1% vs 11.7%; $p < 0.001$). In multivariable analysis, immunocompromise (aOR 4.06, 95% CI 1.71–9.64; $p = 0.001$), age ≥ 60 years (aOR 3.42, 95% CI 1.87–6.25; $p < 0.001$), presence of any comorbidity (aOR 2.18, 95% CI 1.21–3.93; $p = 0.009$), and an interval exceeding 24 months since the last documented dose (aOR 1.94, 95% CI 1.09–3.45; $p = 0.024$) were independently associated with severe disease. Median length of stay was 6 days (IQR 4–9); in-hospital mortality was 2.9% (9/314, 95% CI 1.5–5.4). ***Conclusions:*** In this multicentre case series, severe breakthrough respiratory infection was concentrated among older adults, those with comorbidity or immunocompromise, and those with longer intervals since vaccination. These observations are hypothesis-generating; the absence of an unvaccinated comparison group precludes any inference about vaccine effectiveness.

Keywords: breakthrough infection; vaccine-preventable disease; respiratory tract infections; retrospective studies; India.

INTRODUCTION

Acute respiratory infections remain among the leading causes of morbidity and mortality worldwide, and a substantial proportion are attributable to pathogens for which effective vaccines exist, including Streptococcus pneumoniae, Bordetella pertussis, Haemophilus influenzae type b, influenza viruses, measles virus, and SARS-CoV-2 [1,2]. Expansion of national immunisation programmes has produced large reductions in the incidence and severity of these infections [3]. In India, the Universal Immunisation Programme and subsequent introductions such as pneumococcal conjugate vaccine and the national COVID-19 vaccination drive have substantially altered the epidemiology of respiratory vaccine-preventable disease [4,5]. No vaccine confers absolute protection. Breakthrough infection — clinically apparent infection occurring in a person who has completed an age-appropriate vaccination schedule against the causative pathogen — is an expected consequence of imperfect and waning immunity [6]. Breakthrough episodes arise through several non-exclusive

mechanisms. Primary vaccine failure describes the absence of a protective immune response following an adequate schedule; secondary vaccine failure describes the decay of an initially adequate response over time; antigenic or serotype mismatch describes infection by a strain insufficiently covered by the vaccine formulation; and impaired responses occur in individuals with immunosuppression, extremes of age, or chronic comorbidity [7]. In resource-constrained settings, cold-chain failure and administration error contribute additionally, and may be indistinguishable from true immune escape in routine clinical records [8].

The clinical relevance of these episodes lies in their heterogeneity. Breakthrough disease is frequently, though not invariably, milder than infection in unvaccinated individuals [9]. In specific subgroups — older adults, those with chronic cardiopulmonary or renal disease, and immunocompromised hosts — breakthrough infection may nonetheless result in severe illness requiring intensive care [10,11]. Distinguishing these presentations at the point of triage is difficult, and there is a recognised risk that clinicians are falsely reassured by a documented vaccination history [12]. Published descriptions of breakthrough respiratory infection from South Asia remain limited and are dominated by single-pathogen, single-centre reports, most focused on SARS-CoV-2 during the pandemic period [13].

Few studies describe the broader spectrum of respiratory vaccine-preventable pathogens across both paediatric and adult populations within the same health system, despite the fact that these populations share transmission networks and immunisation infrastructure. Nirmalpur, a large metropolitan area with a mixed public and private hospital ecosystem and documented heterogeneity in immunisation coverage, offers an informative setting in which to characterise this spectrum [14].

We therefore conducted a multicentre retrospective case series across three hospitals. Our objective was to describe the demographic profile, clinical and laboratory characteristics, treatment, and in-hospital outcomes of adults and children who developed breakthrough respiratory vaccine-preventable infections, and to identify patient characteristics associated with severe disease. We did not aim to estimate vaccine effectiveness, which requires a comparison group of unvaccinated patients and cannot be obtained from a case series.

MATERIALS AND METHODS

Study design and reporting

We conducted a multicentre retrospective case series. The study is reported in accordance with the STROBE statement for observational research [15]. The study protocol was not prospectively registered.

Setting

The study was conducted at three hospitals in Hyderabad, Telangana, India. Esra hospital is a 620-bed tertiary teaching hospital with adult and paediatric intensive care units, receiving referrals from across the district. Owaisi hospital is a 340-bed public secondary-care facility serving a predominantly urban catchment of approximately 900,000 residents, with an eight-bed adult intensive care unit. Femcity: Women & Children Hospital is a 180-bed private facility providing obstetric and paediatric care, including a twelve-bed paediatric intensive care unit. Together the three sites recorded approximately 4,100 admissions for acute respiratory illness annually during the study period.

Study period

Records were reviewed for patients admitted between 1 January 2026 and 30 June 2026. This window was selected because it corresponded to the period during which all three sites had migrated to electronic medical records and applied a consistent respiratory pathogen testing panel, and because it spanned three complete respiratory seasons.

Participants and eligibility criteria

Patients of any age were eligible if they presented with an acute respiratory illness and were admitted to a participating hospital during the study period; had laboratory confirmation of infection with a vaccine-preventable respiratory pathogen (SARS-CoV-2, influenza A or B, S. pneumoniae, B. pertussis, H. influenzae type b, or measles virus) by reverse-transcription polymerase chain reaction, blood or pleural fluid culture, or IgM serology as appropriate to the pathogen; had documented vaccination against the identified pathogen with the age-appropriate schedule completed at least 14 days before symptom onset; and had vaccination status verifiable from an immunisation card, a national digital immunisation record, a hospital immunisation register, or a dated entry in the medical record.

Patients were excluded if vaccination status could not be documented from an acceptable source; if patient or caregiver report was the sole basis for vaccination status; if the interval between the final dose and symptom onset was under 14 days; if illness was attributable to a non-vaccine-preventable pathogen alone; if records were incomplete for age, sex, presenting features, or discharge outcome; or if the patient was transferred out within 24 hours, precluding outcome ascertainment.

Data sources and extraction

Data were extracted from electronic medical records and archived paper case sheets using a standardised proforma developed for this study and piloted on 25 records, following which three ambiguous variable definitions were revised. Extraction was performed independently by four trained investigators who were not blinded to the study hypothesis. A random 15% sample of records was re-abstracted by a second investigator; agreement for the primary outcome was excellent (Cohen's $\kappa = 0.91$) and for comorbidity status was good ($\kappa = 0.84$). Discrepancies were resolved by discussion, with unresolved items adjudicated by a senior investigator. Variables collected comprised demographic characteristics; vaccination details including vaccine received, number of doses, dates, interval from last dose to symptom onset, and source of verification; presenting clinical features including symptoms and their duration, vital signs, and oxygen saturation on room air; comorbidities; laboratory and radiological findings; microbiological results; treatment received; and outcomes.

Outcomes

The primary outcome was severe disease as defined in Section 2.5. Secondary outcomes were intensive care admission, duration of respiratory support, length of hospital stay, and in-hospital mortality. Outcomes were prespecified before data extraction began. Comparison between adults and children was prespecified; all other subgroup analyses were post hoc.

Sample size

No a priori sample size calculation was performed. All eligible patients presenting during the study period were included, and the achieved sample size was determined by the number of eligible records available.

Statistical analysis

Continuous variables were summarised as median and interquartile range, distribution having been assessed by the Shapiro–Wilk test and inspection of histograms; categorical variables were summarised as counts and percentages. Between-group comparisons used the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables as appropriate to expected cell counts. Characteristics associated with the primary outcome were examined using multivariable logistic regression. Covariates were selected a priori on clinical grounds and comprised age ≥ 60 years, sex, presence of any comorbidity, immunocompromise, and interval exceeding 24 months since the last documented dose. With 71 events and five covariates, the events-per-variable ratio was 14.2. Robust standard errors clustered by hospital were used to account for non-independence of outcomes within sites [16]. Model discrimination was assessed by the area under the receiver operating characteristic curve and calibration by the Hosmer–Lemeshow test. Effect estimates are reported as adjusted odds ratios with 95% confidence intervals. Missing data were handled by complete-case analysis; missingness exceeded 5% for only two variables (C-reactive protein, 11.8%; chest radiography, 12.1%). A two-sided p-value below 0.05 was considered statistically significant. Given the exploratory nature of the analysis, no adjustment was made for multiple comparisons. Analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Ethics

The study was approved by the Institutional Ethics Committee of Meridian General Hospital, with administrative permission obtained from the two other sites. The requirement for individual informed consent was waived owing to the retrospective use of de-identified records. The study was conducted in accordance with the Declaration of Helsinki and the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants [17].

RESULTS

Patient selection and baseline characteristics

During the study period, 412 patients with laboratory-confirmed respiratory infection due to a vaccine-preventable pathogen were screened. Ninety-eight were excluded: 54 because vaccination status could not be documented from an acceptable source, 19 because the interval between final dose and symptom onset was under 14 days, 17 because records were incomplete for core variables, and 8 because of transfer out within 24 hours. Three hundred and fourteen patients were included in the analysis. The cohort comprised 186 adults (59.2%) and 128 children (40.8%). Median age was 34 years (IQR 6–58; range 0.3–89) and 149 patients (47.5%) were female. Contributions by site were 128 (40.8%) from Meridian General Hospital, 104 (33.1%) from Kalyani Municipal Hospital, and 82 (26.1%) from Sunbird Women and Children's Hospital. At least one comorbidity was present in 141 patients (44.9%), most commonly diabetes mellitus (78, 24.8%), chronic obstructive pulmonary disease (41, 13.1%), and chronic kidney disease (26, 8.3%); 29 patients (9.2%) met criteria for immunocompromise. Baseline characteristics are presented in Table 1.

Table 1: Baseline demographic and clinical characteristics

Characteristic	All (n = 314)	Adults (n = 186)	Children (n = 128)
Age, years, median (IQR)	34 (6–58)	54 (41–67)	5 (2–9)
Female, n (%)	149 (47.5)	84 (45.2)	65 (50.8)
Meridian General, n (%)	128 (40.8)	96 (51.6)	32 (25.0)
Kalyani Municipal, n (%)	104 (33.1)	90 (48.4)	14 (10.9)
Sunbird Women & Children, n (%)	82 (26.1)	0 (0)	82 (64.1)
Any comorbidity, n (%)	141 (44.9)	128 (68.8)	13 (10.2)
Diabetes mellitus, n (%)	78 (24.8)	78 (41.9)	0 (0)
COPD, n (%)	41 (13.1)	41 (22.0)	0 (0)
Chronic kidney disease, n (%)	26 (8.3)	24 (12.9)	2 (1.6)
Immunocompromised, n (%)	29 (9.2)	21 (11.3)	8 (6.3)

Vaccination history

All included patients had documented age-appropriate vaccination against the identified pathogen. The median interval between the final documented dose and symptom onset was 19 months (IQR 11–34), and 108 patients (34.4%) had an interval exceeding 24 months. Ninety-seven patients (30.9%) had received a booster dose. Vaccination status was verified from a national digital immunisation record in 141 patients (44.9%), from a physical immunisation card in 118 (37.6%), and from a hospital immunisation register or dated medical record entry in 55 (17.5%). Vaccination details by pathogen are summarised in Table 2.

Table 2a: Vaccination history by causative pathogen

Pathogen	n (%)	Vaccine received	Median doses	Median interval, last dose to onset, months (IQR)	Interval > 24 months, n (%)	Booster received, n (%)
Influenza A/B	112 (35.7)	Inactivated influenza vaccine	1	8 (5–13)	4 (3.6)	NA†
SARS-CoV-2	96 (30.6)	ChAdOx1 nCoV-19 or BBV152	2	26 (18–34)	58 (60.4)	61 (63.5)
S. pneumoniae	62 (19.7)	PCV13 or PPSV23	3 (children), 1 (adults)	31 (14–52)	34 (54.8)	21 (33.9)
B. pertussis	28 (8.9)	DTwP or DTaP-containing	3	21 (13–33)	5 (17.9)	12 (42.9)
H. influenzae type b	11 (3.5)	Hib conjugate	3	19 (12–28)	2 (18.2)	3 (27.3)
Measles virus	5 (1.6)	MMR or MR	2	42 (36–55)	5 (100.0)	0 (0)
All	**314 (100)**	—	—	**19 (11–34)**	**108 (34.4)**	**97 (30.9)**

† Annual revaccination rather than booster dosing; not applicable

Table 2b: Source of vaccination verification, by pathogen

Pathogen	Digital immunisation record	Physical immunisation card	Hospital register or record entry
Influenza A/B	48	34	30
SARS-CoV-2	71	17	8
S. pneumoniae	12	38	12
B. pertussis	6	19	3
H. influenzae type b	3	7	1
Measles virus	1	3	1
All, n (%)	**141 (44.9)**	**118 (37.6)**	**55 (17.5)**

Causative pathogens

The most frequently identified pathogen was influenza A or B (112, 35.7%), followed by SARS-CoV-2 (96, 30.6%), S. pneumoniae (62, 19.7%), B. pertussis (28, 8.9%), H. influenzae type b (11, 3.5%), and measles virus (5, 1.6%). Co-infection with more than one vaccine-preventable pathogen was identified in 17 patients (5.4%).

The distribution of pathogens differed markedly between adults and children ($p < 0.001$). Among adults, SARS-CoV-2 (78/186, 41.9%) and influenza (64/186, 34.4%) predominated, whereas among children influenza (48/128, 37.5%), B. pertussis (26/128, 20.3%), and S. pneumoniae (21/128, 16.4%) were most frequent. All five measles cases and 26 of 28 pertussis cases occurred in children.

Clinical presentation

The most common presenting symptoms were fever (281, 89.5%), cough (264, 84.1%), breathlessness (138, 43.9%), and sore throat (96, 30.6%). Median duration of symptoms before presentation was 4 days (IQR 3–6). At presentation, median respiratory rate was 24 breaths/min (IQR 20–30) and median oxygen saturation on room air was 95% (IQR 92–97); 89 patients (28.3%) were hypoxaemic ($SpO_2 < 94\%$). Radiographic abnormalities were present in 147 of 276 patients imaged (53.3%), most commonly unilateral consolidation (68, 24.6% of those imaged). Presenting features and laboratory findings are shown in Table 3.

Table 3. Presenting clinical features, laboratory and radiological findings

Variable	All (n = 314)	Adults (n = 186)	Children (n = 128)	p
Symptoms, n (%)				
Fever	281 (89.5)	161 (86.6)	120 (93.8)	0.04
Cough	264 (84.1)	152 (81.7)	112 (87.5)	0.17
Breathlessness	138 (43.9)	101 (54.3)	37 (28.9)	< 0.001
Coryza	118 (37.6)	58 (31.2)	60 (46.9)	0.005
Sore throat	96 (30.6)	64 (34.4)	32 (25.0)	0.07
Wheeze	72 (22.9)	31 (16.7)	41 (32.0)	0.001
Vomiting	49 (15.6)	18 (9.7)	31 (24.2)	< 0.001
Paroxysmal cough	24 (7.6)	3 (1.6)	21 (16.4)	< 0.001
Rash	6 (1.9)	1 (0.5)	5 (3.9)	0.04
Duration and vital signs				
Symptom duration, days, median (IQR)	4 (3–6)	4 (3–7)	3 (2–5)	0.002
Temperature, °C, median (IQR)	38.4 (37.9–39.0)	38.2 (37.8–38.8)	38.7 (38.1–39.3)	< 0.001
Respiratory rate, /min, median (IQR)	24 (20–30)	22 (19–27)	30 (24–38)	< 0.001
Heart rate, /min, median (IQR)	—	96 (84–108)	128 (112–142)	< 0.001
SpO_2 on room air, %, median (IQR)	95 (92–97)	94 (91–97)	96 (94–98)	< 0.001
Hypoxaemia ($SpO_2 < 94\%$), n (%)	89 (28.3)	71 (38.2)	18 (14.1)	< 0.001
Laboratory, median (IQR)				
Leucocyte count, $\times 10^9$/L	9.8 (7.1–13.4)	9.4 (6.9–12.8)	10.6 (7.6–14.2)	0.03
Lymphocyte count, $\times 10^9$/L	1.4 (0.9–2.1)	1.2 (0.8–1.8)	1.9 (1.3–2.7)	< 0.001
C-reactive protein, mg/L ‡	42 (18–88)	51 (24–102)	29 (12–61)	< 0.001
Serum creatinine, mg/dL	0.9 (0.7–1.2)	1.0 (0.8–1.4)	0.5 (0.4–0.6)	< 0.001
Chest imaging				
Imaging performed, n (%)	276 (87.9)	172 (92.5)	104 (81.3)	0.003
Any abnormality, n (% of imaged)	147 (53.3)	98 (57.0)	49 (47.1)	0.11
Unilateral consolidation	68 (24.6)	44 (25.6)	24 (23.1)	—
Bilateral infiltrates	51 (18.5)	41 (23.8)	10 (9.6)	—
Hyperinflation or peribronchial change	21 (7.6)	8 (4.7)	13 (12.5)	—
Pleural effusion	7 (2.5)	5 (2.9)	2 (1.9)	—

‡ Measured in 277 patients (missing in 37, 11.8%).

Management

Antimicrobial therapy was administered to 248 patients (79.0%), antiviral therapy to 121 (38.5%), and systemic corticosteroids to 94 (29.9%). Respiratory support of any kind was required by 141 patients (44.9%): low-flow supplemental oxygen alone in 70 (22.3%), high-flow nasal cannula or non-invasive ventilation in 54 (17.2%), and invasive mechanical ventilation in 17 (5.4%).

Primary outcome

Severe disease occurred in 71 of 314 patients (22.6%, 95% CI 18.2–27.5). Severe disease was substantially more frequent in adults than in children (56/186, 30.1% vs 15/128, 11.7%; $p < 0.001$). In unadjusted analysis, age ≥ 60 years, presence of any comorbidity, immunocompromise, an interval exceeding 24 months since the last dose, and hypoxaemia at presentation were each associated with severe disease (Table 4). In the multivariable logistic regression model, immunocompromise

showed the strongest independent association with severe disease (aOR 4.06, 95% CI 1.71–9.64; p = 0.001), followed by age ≥ 60 years (aOR 3.42, 95% CI 1.87–6.25; p < 0.001), presence of any comorbidity (aOR 2.18, 95% CI 1.21–3.93; p = 0.009), and an interval exceeding 24 months since the last documented dose (aOR 1.94, 95% CI 1.09–3.45; p = 0.024). Male sex was not associated with severe disease after adjustment (aOR 1.21, 95% CI 0.70–2.09; p = 0.49). Model discrimination was acceptable (area under the curve 0.78, 95% CI 0.72–0.84) and calibration adequate (Hosmer–Lemeshow p = 0.41).

Table 4: Associations with severe disease

Variable	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Immunocompromise	5.12 (2.29–11.45)	< 0.001	4.06 (1.71–9.64)	0.001
Age ≥ 60 years	4.18 (2.41–7.25)	< 0.001	3.42 (1.87–6.25)	< 0.001
Any comorbidity	3.06 (1.76–5.32)	< 0.001	2.18 (1.21–3.93)	0.009
Interval > 24 months	2.31 (1.35–3.95)	0.002	1.94 (1.09–3.45)	0.024
Male sex	1.34 (0.79–2.27)	0.28	1.21 (0.70–2.09)	0.49

Secondary outcomes

Intensive care admission was required by 48 patients (15.3%). Median duration of respiratory support among those receiving it was 4 days (IQR 2–7). Median length of hospital stay was 6 days (IQR 4–9) overall, and was longer among patients with severe disease than among those without (11 days, IQR 8–16, vs 5 days, IQR 3–7; p < 0.001). In-hospital mortality was 9 of 314 (2.9%, 95% CI 1.5–5.4). Seven deaths occurred in adults aged ≥ 60 years with at least one comorbidity, and two in immunocompromised children. All nine deaths occurred among patients meeting the primary outcome definition; case fatality among patients with severe disease was 12.7% (9/71).

DISCUSSION

Principal findings

In this multicentre retrospective case series of 314 adults and children with breakthrough respiratory vaccine-preventable infection, 22.6% met the criterion for severe disease and in-hospital mortality was 2.9%. Severe disease was concentrated among immunocompromised patients, older adults, those with comorbidity, and those in whom a longer interval had elapsed since the last documented vaccine dose. Adults experienced severe disease more than twice as often as children, and the pathogen distribution differed substantially between the two groups. These findings indicate that a documented vaccination history does not exclude the possibility of severe respiratory illness, particularly in older and immunocompromised patients.

Comparison with existing literature

The proportion of patients with severe disease in our cohort is broadly consistent with hospital-based breakthrough series reported from comparable settings, in which severity among vaccinated inpatients has been described in a similar range [18]. This concordance is expected, since all such series share a restriction to hospitalised patients and are therefore enriched for severe presentations relative to the community. Our observation that immunocompromise carried the strongest independent association with severe disease is consistent with reports across multiple respiratory pathogens, in which impaired humoral and cell-mediated responses to vaccination have been documented [10]. The magnitude of the association we observed is somewhat larger than in several published series, which may reflect our relatively broad definition of immunocompromise and the small number of such patients in our cohort, reflected in the wide confidence interval. By contrast, our finding of an association between longer interval since the last dose and severe disease differs from [11], which reported no such gradient. Plausible explanations include differences in the vaccines and pathogens contributing to each cohort, since waning kinetics differ markedly between conjugate polysaccharide vaccines and inactivated viral vaccines; differences in booster uptake, which was 30.9% in our cohort; and residual confounding by age, since older patients in our cohort were also more likely to have longer intervals since vaccination. The adult–child contrast merits particular attention, since few published series encompass both populations within one health system. The predominance of pertussis and measles among children in our cohort, against a predominance of SARS-CoV-2 and influenza among adults, reflects the different positions of the two groups within the immunisation schedule: children are typically closer in time to their primary series but are exposed to pathogens for which schedule completion and booster timing remain incomplete at the population level, whereas adults are typically further from their last dose and carry a greater burden of comorbidity [19]. The lower proportion of severe disease among children is consistent with this and with the general observation that comorbidity burden, rather than age alone, drives severity in breakthrough disease [10].

Interpretation and possible mechanisms

Several non-exclusive mechanisms may account for the pattern observed. First, waning immunity is a plausible contributor: the median interval from final dose to symptom onset was 19 months, and an interval exceeding 24 months was

independently associated with severe disease, which is consistent with the recognised decline in humoral protection following several of the vaccines represented in this cohort [7]. Second, antigenic or serotype mismatch may explain a proportion of episodes, particularly among influenza and pneumococcal cases; we did not perform subtyping or serotyping, and this mechanism cannot be assessed from our data [20,21]. Third, host factors are established determinants of impaired vaccine response and may account for the concentration of severe outcomes among immunocompromised and comorbid patients [11]. Fourth, in settings where cold-chain integrity and documentation quality vary, a proportion of episodes classified as breakthrough may reflect impaired vaccine potency or misclassified vaccination status rather than true immune escape [8]. These mechanisms cannot be distinguished with the data available. We did not measure antibody titres, and the design does not permit attribution of individual episodes to any specific mechanism. The associations reported here are observational and hypothesis-generating.

Clinical and public health implications

The independent association between immunocompromise and severe disease, together with the observation that all nine deaths occurred among patients who were either older adults with comorbidity or immunocompromised children, supports the clinical practice of stratifying vaccinated patients by host factors rather than by vaccination status alone at the point of triage. A documented vaccination history should not lower the threshold for admission or for close monitoring in these subgroups. The association with interval since last dose is consistent with the rationale for booster programmes but does not, on its own, establish the appropriate booster interval or target group. Determining that requires effectiveness studies with unvaccinated or test-negative comparators, and we would caution explicitly against citing a case series of this design in support of a change to immunisation schedules. We emphasise that these findings must not be interpreted as evidence that vaccination is ineffective. A case series of vaccinated patients contains no unvaccinated comparison group and therefore cannot estimate vaccine effectiveness; the absence of unvaccinated cases from this analysis reflects the eligibility criteria, not the epidemiology of the disease [15].

Strengths and limitations

Strengths: The study draws on three hospitals with differing case mix, including a dedicated women's and children's facility, permitting description of breakthrough infection across the full age range within a single metropolitan health system. Vaccination status was verified against documentary sources rather than patient report, reducing misclassification of the exposure that defines the cohort. Data extraction used a piloted standardised proforma with duplicate abstraction of a random subsample and good to excellent inter-rater agreement.

Limitations: First, the retrospective design constrained us to variables recorded for clinical purposes; residual confounding by unmeasured factors — including socioeconomic status, nutritional status, delay in healthcare-seeking, and tobacco or biomass smoke exposure — cannot be excluded. Second, as a case series without an unvaccinated comparison group, the study cannot estimate vaccine effectiveness or support causal inference; all associations are descriptive. Third, restriction to hospitalised patients introduces selection bias towards severe disease, and the reported proportions do not represent the severity distribution of breakthrough infection in the community. Fourth, all three sites are in a single metropolitan area, limiting generalisability to rural populations and to states with different immunisation coverage and vaccine product profiles. Fifth, 54 patients (13.1% of those screened) were excluded because vaccination status could not be documented, and these patients may differ systematically from those included. Sixth, six distinct pathogens were pooled in a single analysis of severity despite differing natural histories and vaccine mechanisms; the resulting estimates should be regarded as averaged across a heterogeneous cohort. Seventh, subtyping and serotyping were not performed, precluding assessment of antigenic mismatch. Eighth, multiple comparisons were made without correction and secondary findings should be regarded as exploratory.

Future research

Prospective test-negative or case-control designs with contemporaneous comparators are required to estimate vaccine effectiveness in this population. Serological studies linking antibody titre at presentation to clinical severity would help distinguish waning immunity from primary vaccine failure, and systematic serotyping or genotyping of isolates would clarify the contribution of antigenic mismatch. Pathogen-specific analyses in larger cohorts would address the heterogeneity that limits the present study, and multi-state studies incorporating rural sites and community-managed cases are needed to establish whether the pattern described here generalises beyond a metropolitan hospital population.

CONCLUSION

In this multicentre retrospective case series, breakthrough respiratory vaccine-preventable infections requiring hospitalisation occurred across the age range and resulted in severe disease in 22.6% of patients. Immunocompromise, age ≥ 60 years, comorbidity, and a longer interval since the last documented vaccine dose were each independently associated with severe outcome. A documented vaccination history should not by itself reduce clinical suspicion of severe respiratory illness, particularly in older and immunocompromised patients. Because the design lacks an unvaccinated comparison

group, these findings describe the clinical profile of breakthrough disease rather than the performance of vaccination, and prospective controlled studies are required before the observed associations can inform immunisation policy.

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