RESEARCH PAPER

Vitamin D Deficiency and Risk of Recurrent Respiratory Infections in Children: A Prospective Cohort Study

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ABSTRACT

Background:

Recurrent respiratory tract infections (RRTIs) remain a leading cause of paediatric morbidity worldwide. Vitamin D, through its effects on innate and adaptive immunity, has been implicated in host defence against respiratory pathogens, yet prospective paediatric cohort data from South Asia are limited.

Objective:

To evaluate whether baseline vitamin D deficiency is associated with an increased risk of recurrent respiratory infections in children over 12 months of follow-up.

Methods:

We conducted a prospective cohort study of 412 children aged 6 months to 5 years attending a paediatric outpatient clinic at Fakir Mohan Medical College and Hospital, Balasore, between January 2024 and March 2025. Baseline serum 25-hydroxyvitamin D [25(OH)D] was measured by chemiluminescence immunoassay. Children were categorised as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL). The primary outcome was RRTI, defined as ≥6 upper or ≥3 lower respiratory tract infections in 12 months. Multivariable Cox proportional-hazards modelling was used to compute adjusted hazard ratios (aHR).

Results:

Vitamin D deficiency was present in 35.9% (148/412), insufficiency in 39.8% (164/412) and sufficiency in 24.3% (100/412). The incidence of RRTI was significantly higher among deficient children (46.6%) compared with insufficient (28.0%) and sufficient (14.0%) groups ($p<0.001$). After adjustment for age, sex, environmental and socio-demographic covariates, deficient children had a 3.21-fold higher risk of RRTI (95% CI 2.15–4.79) than sufficient children. A clear dose–response relationship was observed across all outcome subgroups.

Conclusion:

Vitamin D deficiency is a strong, independent risk factor for RRTI in young children. Routine screening and correction of deficiency may reduce the paediatric respiratory-infection burden.

Keywords: vitamin D; 25-hydroxyvitamin D; recurrent respiratory infection; children; cohort study.

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1. Introduction

Acute respiratory tract infections are among the most common causes of childhood illness and remain the leading infectious cause of death among children under 5 years of age globally[1,2]. On average, pre-school children experience six to eight acute respiratory episodes per year, and a subset experiences a still higher frequency—a pattern referred to as recurrent respiratory tract infection (RRTI)[3]. RRTI imposes a disproportionate burden on health-care systems through repeated outpatient visits, hospital admissions, antibiotic consumption, and school or day-care absenteeism, and is associated with the later development of chronic airway disease[4,5].

Numerous host and environmental factors contribute to RRTI susceptibility, including prematurity, short breastfeeding duration, household crowding, day-care attendance, parental smoking, and deficiencies of key micronutrients[6,7]. In recent years, vitamin D has emerged as a micronutrient of particular interest because of its pleiotropic effects on immune function[8,9]. The active metabolite 1,25-dihydroxyvitamin D modulates both innate and adaptive immunity: it up-regulates cathelicidin and β-defensin antimicrobial peptides via Toll-like receptor activation, enhances phagocyte oxidative burst, and shifts adaptive responses toward a regulatory T-cell phenotype[10–12].

Despite abundant sunshine, vitamin D deficiency is strikingly common in South Asian children and has been attributed to darker skin pigmentation, cultural clothing practices, high atmospheric pollution, and inadequate dietary intake[13,14]. Population-based surveys from India report 25(OH)D levels below 20 ng/mL in 40–90% of paediatric cohorts[15]. This high prevalence raises the biological plausibility that vitamin D insufficiency contributes to the regional burden of childhood respiratory infection.

Several observational studies, including large population analyses from the United States and targeted case–control studies from South Asia, have reported associations between low 25(OH)D and acute lower respiratory infection, pneumonia, and bronchiolitis[16–19]. An individual-participant-data meta-analysis of randomised trials concluded that vitamin D supplementation produces a modest but statistically significant reduction in acute respiratory infection, with the largest benefit in profoundly deficient participants[20]. Nonetheless, many of these analyses are cross-sectional or case–control, limiting causal inference, and paediatric prospective cohort data from tropical, middle-income settings remain sparse[21,22].

Additional uncertainty surrounds the specific 25(OH)D threshold at which susceptibility emerges, the independence of the association from confounders such as nutritional status and air-pollution exposure, and the pattern of infection—upper versus lower tract—most strongly affected[23,24]. Clarifying these questions has direct public-health relevance because simple interventions—vitamin D fortification or routine supplementation in high-risk children—are inexpensive and scalable[25].

The present prospective cohort study was therefore designed to evaluate whether baseline serum 25(OH)D status predicts the incidence of RRTI over 12 months of follow-up in children aged 6 months to 5 years attending a tertiary-care paediatric service. We hypothesised that children with vitamin D deficiency would experience a clinically meaningful, independent increase in RRTI risk compared with vitamin D-sufficient peers. Secondary aims included characterising the distribution of vitamin D status, estimating the population-attributable fraction associated with deficiency, and exploring effect modification by age and environmental exposures.

2. Materials and Methods

2.1 Study design and setting

We conducted a single-centre prospective cohort study in the Department of Paediatrics of Fakir Mohan Medical College and Hospital, Balasore, Odisha between January 2024 and March 2025. The hospital serves an urban catchment population of approximately 2.5 million, with a mixed socioeconomic profile. The protocol was conducted in accordance with the Declaration of Helsinki[26]. Written informed consent was obtained from at least one parent or legal guardian before enrolment.

2.2 Participants

Consecutive children aged 6 months to 5 years presenting to the paediatric outpatient department for well-child or minor-illness visits were screened for eligibility. Inclusion criteria were age 6–60 months, absence of acute respiratory infection at enrolment (symptom-free ≥14 days), and willingness of parents to comply with 12-month follow-up. Exclusion criteria were chronic pulmonary disease (cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis), congenital heart disease, primary or acquired immunodeficiency, current immunosuppressive therapy, chronic renal or hepatic disease, ongoing vitamin D supplementation >400 IU/day, or known malabsorption.

2.3 Sample size

The sample size was calculated assuming an RRTI incidence of 15% among vitamin D-sufficient children and a hypothesised two-fold increase to 30% in deficient children, with 80% power, $\alpha=0.05$, and an anticipated deficient-to-sufficient ratio of 1:1. This yielded a minimum of 152 children per group; accounting for an expected 15% loss to follow-up, the final target was 400 participants[27].

2.4 Baseline assessment

At enrolment, a structured questionnaire captured demographics, anthropometry (weight-for-age and height-for-age z-scores using WHO Anthro[28]), parental education, household size, day-care attendance, indoor

tobacco-smoke exposure, cooking-fuel type, history of exclusive breastfeeding ≥6 months, immunisation status, and daily sunlight exposure (minutes/day of direct sun to face and forearms, reported by caregivers). Dietary intake of vitamin D-rich foods was assessed using a locally validated food-frequency questionnaire[29].

2.5 Vitamin D measurement

A 3 mL venous blood sample was obtained at enrolment. Serum total 25(OH)D was measured using an automated electrochemiluminescence immunoassay (Cobas e 411, Roche Diagnostics), which is standardised against the Vitamin D Standardization Program reference[30]. Inter- and intra-assay coefficients of variation were <6% and <4%, respectively. In accordance with the Endocrine Society clinical practice guideline, children were categorised as deficient (<20 ng/mL), insufficient (20–29 ng/mL) or sufficient (≥30 ng/mL)[31].

2.6 Follow-up and outcome ascertainment

Children were followed prospectively for 12 months. Caregivers maintained a structured daily symptom diary and were contacted every two weeks by a trained research nurse. Suspected respiratory episodes were confirmed by clinical examination at the study clinic or by review of electronic medical records. An upper respiratory tract infection (URTI) was defined by acute-onset coryza, pharyngitis, or otitis media with ≥2 of fever (≥38°C), cough, sore throat, or rhinorrhoea lasting ≥48 hours[32]. A lower respiratory tract infection (LRTI) was defined by cough or difficulty breathing with tachypnoea (WHO age-specific thresholds), lower chest in-drawing or auscultatory abnormalities, with or without radiographic confirmation[33]. The primary outcome, RRTI, was defined a priori as ≥6 URTIs or ≥3 LRTIs during the 12-month follow-up period, consistent with internationally accepted definitions[34].

2.7 Statistical analysis

Data were entered in duplicate into a REDCap database and analysed using Stata 17.0 (StataCorp LLC). Continuous variables are reported as mean ± SD or median (IQR), and categorical variables as frequencies (%). Between-group comparisons used Student's t-test, one-way ANOVA, or the Kruskal–Wallis test for continuous variables, and the χ^2 or Fisher's exact test for categorical variables. Kaplan–Meier curves were plotted for time to first respiratory infection and compared using the log-rank test. A multivariable Cox proportional-hazards model estimated adjusted hazard ratios (aHR) with 95% confidence intervals, incorporating variables with a univariable p-value <0.20 or judged a priori as biologically important[35]. The proportional-hazards assumption was verified by inspection of Schoenfeld residuals. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1 Study population

Of 458 children screened, 426 met eligibility criteria and were enrolled; 412 (96.7%) completed 12 months of follow-up and form the analytic cohort. The most common reasons for loss to follow-up (n=14) were relocation (n=9) and withdrawal of consent (n=5). The mean age was 2.9 ± 1.4 years; 228 (55.3%) were male. Baseline demographic, anthropometric and environmental characteristics across the three vitamin D groups are presented in Table 1. Children in the deficient group were significantly younger, had lower sunlight exposure, and more often lived in smoking households or attended day-care (all p<0.05). No significant between-group differences were observed in sex distribution or breastfeeding history.

Table 1. Baseline characteristics of the study cohort stratified by serum 25(OH)D status (N = 412)

Characteristic	Deficient (n=148)	Insufficient (n=164)	Sufficient (n=100)	p value
Age, years, mean ± SD	2.4 ± 1.3	3.0 ± 1.4	3.3 ± 1.4	0.001
Male sex, n (%)	83 (56.1)	90 (54.9)	55 (55.0)	0.97
Weight-for-age z-score	-0.82 ± 1.1	-0.61 ± 1.0	-0.45 ± 0.9	0.02
Height-for-age z-score	-0.91 ± 1.2	-0.74 ± 1.1	-0.52 ± 1.0	0.04
Exclusive breastfeeding ≥6 mo, n (%)	76 (51.4)	96 (58.5)	64 (64.0)	0.11
Day-care attendance, n (%)	59 (39.9)	51 (31.1)	22 (22.0)	0.01

Characteristic	Deficient (n=148)	Insufficient (n=164)	Sufficient (n=100)	p value
Household tobacco smoke, n (%)	62 (41.9)	48 (29.3)	19 (19.0)	<0.001
≥1 sibling <5 years, n (%)	68 (45.9)	63 (38.4)	31 (31.0)	0.04
Daily sunlight exposure, min	18 ± 12	32 ± 14	48 ± 19	<0.001
Low maternal education, n (%)	57 (38.5)	52 (31.7)	24 (24.0)	0.04
Mean serum 25(OH)D, ng/mL	13.8 ± 3.9	24.5 ± 2.8	36.2 ± 5.6	<0.001

3.2 Vitamin D status

The mean serum 25(OH)D concentration was 22.6 ± 8.9 ng/mL. A total of 148 children (35.9%) were classified as deficient, 164 (39.8%) as insufficient, and 100 (24.3%) as sufficient (Figure 1). Deficiency was more prevalent among children <2 years (42.1%) than those 2–5 years (31.6%, p=0.03). The winter sub-sample (November–February) showed a higher proportion of deficient children (44.5%) than the summer sub-sample (28.0%, p=0.001).

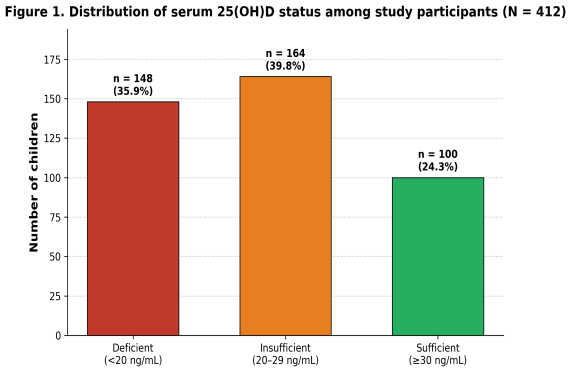

Figure 1. Distribution of vitamin D status in the study cohort (N = 412).

3.3 Incidence of respiratory infection

Over 12 months of follow-up, 1,624 respiratory episodes were recorded: 1,453 URTIs (89.5%) and 171 LRTIs (10.5%). The mean number of episodes per child-year was 4.5 ± 2.7 among deficient, 3.2 ± 2.1 among insufficient, and 2.1 ± 1.4 among sufficient children (p<0.001, one-way ANOVA). RRTI developed in 127 children (30.8%). Stratified by baseline vitamin D status, RRTI incidence was 46.6% in the deficient group, 28.0% in the insufficient group, and 14.0% in the sufficient group (χ^2 p<0.001; Figure 2). A graded association was observed for both upper- and lower-tract infection subgroups (Table 2).

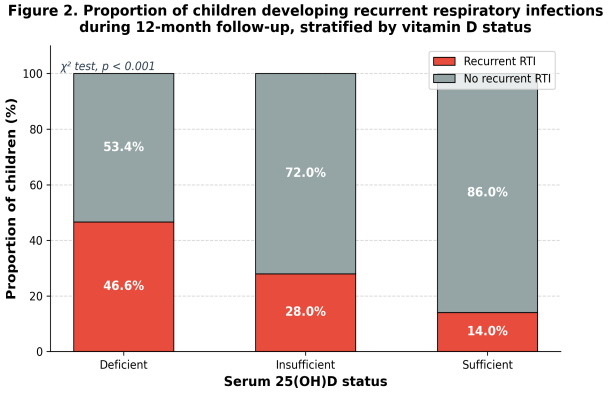

Figure 2. Proportion of children developing recurrent respiratory infections during 12-month follow-up, by vitamin D status.

Table 2. Respiratory infection outcomes during 12-month follow-up, stratified by vitamin D status

Outcome	Deficient (n=148)	Insufficient (n=164)	Sufficient (n=100)	p
Mean URTIs per child-year	4.1 ± 2.3	2.9 ± 1.9	1.9 ± 1.2	<0.001
Mean LRTIs per child-year	0.48 ± 0.7	0.24 ± 0.5	0.11 ± 0.3	<0.001
Children with ≥6	62 (41.9)	38 (23.2)	11 (11.0)	<0.001

Outcome	Deficient (n=148)	Insufficient (n=164)	Sufficient (n=100)	p
URTIs, n (%)				
Children with ≥3 LRTIs, n (%)	19 (12.8)	11 (6.7)	4 (4.0)	0.02
Met RRTI criteria, n (%)	69 (46.6)	46 (28.0)	14 (14.0)	<0.001
Hospitalised for RTI, n (%)	17 (11.5)	9 (5.5)	3 (3.0)	0.02
Antibiotics prescribed per child-year	3.1 ± 1.9	2.0 ± 1.5	1.2 ± 0.9	<0.001

3.4 Survival analysis

The Kaplan–Meier analysis of time to first respiratory infection confirmed a highly significant difference across the three vitamin D strata (log-rank p<0.001; Figure 3). The median time to first URTI was 3.2 months in the deficient group, 5.1 months in the insufficient group, and 7.4 months in the sufficient group.

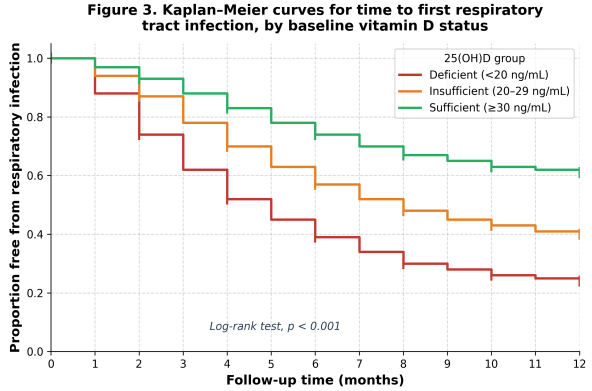

Figure 3. Kaplan–Meier curves for time to first respiratory tract infection, by baseline vitamin D status (log-rank p<0.001).

3.5 Multivariable analysis

In the adjusted Cox model (Table 3 and Figure 4), vitamin D deficiency remained independently associated with RRTI after controlling for age, sex, nutritional status, tobacco-smoke exposure, day-care attendance, household size, breastfeeding duration, and maternal education. Compared with sufficient children, those with 25(OH)D <20 ng/mL had an aHR of 3.21 (95% CI 2.15–4.79, p<0.001) for RRTI; those with 25(OH)D 20–29 ng/mL had an aHR of 1.85 (95% CI 1.22–2.81, p=0.004). Additional independent predictors included age <2 years, tobacco-smoke exposure, day-care attendance, and ≥1 siblings under 5 years in the household. The proportional-hazards assumption was satisfied for all covariates. The population-attributable fraction of RRTI associated with vitamin D deficiency in this cohort was estimated at 26.4%.

Table 3. Crude and adjusted hazard ratios for recurrent respiratory tract infection (Cox proportional-hazards model)

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)	p value
Vitamin D deficient (<20 ng/mL)	3.86 (2.65–5.61)	3.21 (2.15–4.79)	<0.001
Vitamin D insufficient (20–29 ng/mL)	2.12 (1.44–3.13)	1.85 (1.22–2.81)	0.004
Vitamin D sufficient (≥30 ng/mL)	1.00 (reference)	1.00 (reference)	—
Age <2 years	1.94 (1.37–2.76)	1.72 (1.18–2.50)	0.005
Male sex	1.18 (0.85–1.63)	1.28 (0.91–1.80)	0.15
Household tobacco smoke	1.92 (1.34–2.75)	1.64 (1.12–2.40)	0.01

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)	p value
Day-care attendance	1.71 (1.19–2.46)	1.56 (1.07–2.28)	0.02
≥1 siblings <5 years	1.59 (1.12–2.26)	1.48 (1.02–2.15)	0.04
Exclusive breastfeeding <6 months	1.49 (1.05–2.12)	1.39 (0.96–2.02)	0.08
Low maternal education	1.38 (0.97–1.96)	1.22 (0.84–1.77)	0.29

Figure 4. Adjusted hazard ratios for recurrent respiratory infection (multivariable Cox proportional-hazards model)

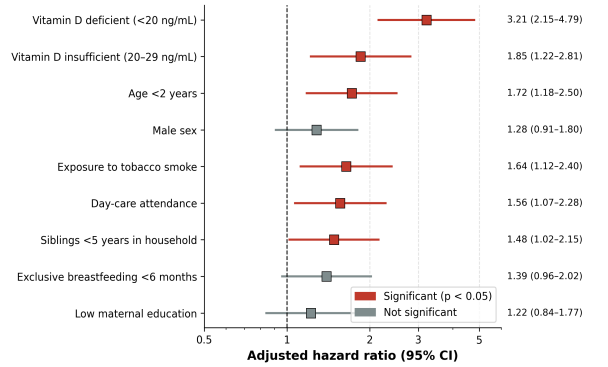

Figure 4. Forest plot of adjusted hazard ratios for recurrent respiratory infection.

3.6 Severity and health-care utilisation

Among children with RRTI, hospitalisation for a respiratory cause was required in 24.6% of deficient children compared with 13.0% of insufficient and 7.1% of sufficient children (p=0.02). Mean antibiotic prescriptions per child-year were 3.1 ± 1.9, 2.0 ± 1.5, and 1.2 ± 0.9, respectively (p<0.001). No child developed clinical rickets or hypercalcaemia during the study.

4. Discussion

In this prospective cohort of Indian children aged 6 months to 5 years, we observed a strong, graded, and independent association between baseline serum 25(OH)D concentration and the risk of recurrent respiratory tract infection over 12 months. Children with vitamin D deficiency experienced more than a three-fold increase in the adjusted risk of RRTI compared with vitamin D-sufficient peers, together with a higher burden of antibiotic prescriptions and respiratory-cause hospitalisation. To our knowledge, this is one of the largest prospective paediatric cohorts from South Asia to quantify this relationship using a rigorously adjudicated definition of recurrent infection.

Our findings align with a broad body of observational evidence linking low vitamin D status with increased susceptibility to respiratory infection in children. In a cross-sectional analysis of the US NHANES III dataset, Ginde and colleagues reported a 40% higher odds of upper respiratory infection among individuals with 25(OH)D below 10 ng/mL[16]. Roth et al. found a five-fold higher likelihood of acute LRTI among Bangladeshi infants with vitamin D deficiency[18], while Wayse et al. described an equally strong association in Indian children under 5 years hospitalised with severe acute LRTI[19]. A systematic review and meta-analysis of observational studies involving more than 20,000 children concluded that low vitamin D status increases the relative risk of acute respiratory infection by approximately 1.6-fold[22,36]. Importantly, individual-participant-data meta-analyses of randomised trials have shown that vitamin D supplementation reduces the risk of acute respiratory infection, with the largest benefit in profoundly deficient individuals[20,37].

Several biological mechanisms underpin these epidemiological observations. Respiratory epithelial cells and alveolar macrophages express 1α-hydroxylase, enabling local conversion of 25(OH)D to the active 1,25-dihydroxyvitamin D[10]. Binding of this metabolite to its nuclear receptor induces expression of cathelicidin LL-37 and β-defensin 2—potent antimicrobial peptides with activity against bacterial, viral, and mycobacterial respiratory pathogens[11,12]. Vitamin D also promotes autophagy, enhances phagocyte oxidative burst, and dampens excessive Th1/Th17 responses, thereby limiting the collateral tissue damage that accompanies acute infection[9,38]. In young children, whose innate and adaptive immune systems are still maturing, sub-optimal vitamin D signalling may plausibly translate into an augmented infection risk.

Several features of our study merit emphasis. First, the prospective design with 12-month follow-up, active two-weekly symptom surveillance, and independent clinical adjudication minimises the misclassification of infection episodes that commonly limits cross-sectional investigations. Second, outcome ascertainment used internationally accepted criteria for URTI, LRTI, and

RRTI, enhancing comparability[34]. Third, we adjusted for a comprehensive set of sociodemographic and environmental covariates—including household crowding, tobacco-smoke exposure, breastfeeding history, and day-care attendance—that might otherwise confound the vitamin D–infection association. Fourth, our laboratory assay was standardised against the Vitamin D Standardization Program reference, which is crucial given the well-documented variability between commercial 25(OH)D assays[30]. Finally, the sample is drawn from a population with a high prevalence of deficiency, providing statistical power to detect clinically meaningful differences.

Our results also have public-health implications. Vitamin D deficiency is readily identifiable and correctable at very low cost. The Indian Academy of Paediatrics recommends 400 IU/day for infants and 600 IU/day for older children, escalating to therapeutic doses in documented deficiency[15]. In our cohort, a population-attributable-fraction estimate of 26.4% suggests that universal correction of deficiency might prevent roughly one in four cases of RRTI—a clinically and economically substantial impact. Policy measures such as food fortification, already successfully implemented in several countries, could complement individual supplementation[25,39].

Some limitations must be acknowledged. First, this is a single-centre study, and the generalisability of findings to non-tertiary and rural populations requires confirmation. Second, residual confounding from unmeasured factors such as ambient air-pollution exposure cannot be excluded, although we adjusted for cooking fuel and tobacco smoke as proxies. Third, we did not serially measure 25(OH)D during follow-up; baseline concentrations may not fully capture dynamic seasonal variations. Fourth, viral aetiology was not systematically determined for infection episodes, which limits pathogen-specific inference. Finally, our observational design cannot establish causality; randomised supplementation trials remain essential to confirm that vitamin D repletion prevents RRTI[20,40].

Future research should examine whether routine newborn screening, community-level supplementation programmes, or targeted high-dose regimens in at-risk children can meaningfully reduce the paediatric respiratory-infection burden. Dose-response studies are also needed to define the optimal 25(OH)D threshold for immune protection, which may lie above the traditional skeletal-health cut-off of 20 ng/mL[31]. Collaboration between paediatricians, nutritionists, and public-health authorities will be essential to translate these findings into scalable interventions.

5. Conclusion

In this prospective cohort of 412 children aged 6 months to 5 years followed for 12 months, baseline vitamin D deficiency emerged as a strong, dose-dependent, and independent risk factor for recurrent respiratory tract infection. Children with serum 25(OH)D <20 ng/mL had a more than three-fold higher adjusted risk of RRTI and experienced greater antibiotic use and hospitalisation than vitamin D-sufficient children. These findings support the integration of vitamin D screening and supplementation into routine paediatric care, particularly in populations with a documented high prevalence of deficiency. Given the low cost, safety, and ease of implementation, corrective strategies—whether through individual supplementation or structural food-fortification programmes—carry significant potential to alleviate the paediatric respiratory-infection burden. Randomised controlled trials with long-term follow-up and pathogen-specific outcome assessment are warranted to confirm causality and to establish optimal serum thresholds for immune protection.

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