Stability and age-specific patterns of rhinovirus circulation in children observed over 3 decades

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Background: Rhinoviruses (RV) are the most common respiratory viruses globally and a major cause of airway symptoms in children and individuals with asthma. Although more than 170 RV types exist across 3 species (RV-A, RV-B, RV-C), type-specific circulation patterns and age-related prevalence remain poorly defined.

Objective: We characterized long-term circulation patterns, age-specific prevalence, and host genetic associations of RV types using a large pediatric dataset.

Methods: We retrospectively analyzed 12,697 RV infections identified by PCR and partial sequencing from 11,960 nasal samples collected between 1997 and 2025 across 20 pediatric populations in Finland, Australia, and the United States, including 10 National Institutes of Health ECHO cohort sites. RV types were classified by species, and host CDHR3 rs6967330 genotype, which impacts RV-C receptor binding, was available for a subset. Temporal stability, phylogenetic clustering, and detection frequency by age were assessed by stream graph visualization, slope modeling, and Spearman correlation.

Results: RV type circulation was remarkably stable over 3 decades; 97% of types had slope estimates whose 95% confidence intervals included zero, indicating no significant temporal change. Commonly detected types did not consistently cluster phylogenetically, suggesting that capsid sequence similarity does not fully explain fitness. Certain types (eg, A36, A101, C15) were prevalent across all pediatric age groups, whereas others (eg, C2, C40, A78, A12) were more frequent in younger children. The CDHR3 rs6967330-A risk allele was associated with increased overall RV-C infection but it did not alter the distribution of common versus rare RV-C types.

Conclusion: RV type prevalence and age-specific patterns have remained stable for decades, supporting targeted interventions focused on consistently circulating types and those most common in young children. (J Allergy Clin Immunol 2026;■■■:■■■-■■■.)

Key words: *Rhinovirus epidemiology, virus circulation patterns, pediatric respiratory infections, age-specific prevalence, CDHR3 genotype, viral phylogenetics, respiratory virus stability, vaccine development, antiviral targets, NIH ECHO cohort*

Rhinoviruses (RV) represent the most common etiology of the common cold.[1,2] Most symptomatic RV infections present with typical upper respiratory symptoms including pharyngitis, cough, rhinorrhea, and fever. RV infections can provoke severe lower respiratory symptoms in certain patient populations. In infants and preschoolers, RV can cause severe respiratory distress in the form of infantile bronchiolitis, wheezing illnesses, and pneumonia.[1,3,4] In children and adults with asthma, RV infections are a common trigger for acute exacerbations that may require hospital and intensive care unit admissions for respiratory support.[5,6] In older adults, RV can also exacerbate chronic obstructive pulmonary disease.[7]

The RV capsid surface is formed by the VP1, VP2, and VP3 proteins, which are exposed to the host immune system and serve as the primary antigenic determinants for neutralizing antibodies.[8,9] Variability in these surface proteins drives the extensive genotypic diversity observed among RVs.[10-12] Since their

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Abbreviations used
CDHR3: Cadherin-related family member 3
CI: Confidence interval
ECHO: Environmental Influences on Child Health Outcomes
RV: Rhinovirus
RV-A/B/C: RV species A, B, and C
VP1-4: Viral capsid proteins 1-4

discovery in 1956, approximately 170 distinct RV types have been identified and classified into 3 species in the genus *Enterovirus: alpharhino* (RV-A), *betarhino* (RV-B), and *cerhino* (RV-C).[13,14] Whereas most RV-A and RV-B types were originally defined by serotyping, the relationship between genetic and antigenic diversity in RV-C remains less well defined because its classification is based primarily on sequence divergence in capsid-coding regions. Emerging data suggest that most genetically assigned RV-C types likely represent distinct serotypes, although some closely related RV types may exhibit antigenic overlap.[11,12]

Despite its significant global health care burden, there is limited information about RV epidemiology. At the species level, we and others have previously demonstrated that RV-C infections are more virulent than other RV species and are also especially prevalent in young children[15-17] as well as in those with a polymorphism in the cadherin-related family member 3 (*CDHR3*) gene,[18] which encodes the cellular receptor. Individual studies and meta-analyses suggest that some RV types might be more common than others.[17,19,20] However, the broad genetic diversity of RVs, combined with the absence of national or global surveillance systems—unlike those established for some other respiratory viruses—has significantly hindered our ability to understand the circulation dynamics of individual RV types over time. Identifying the most prevalent RV types and the age groups they most commonly affect is essential for informing future therapeutic strategies and mitigating the substantial disease burden caused by these ubiquitous viruses across all age groups.[15,21]

To address this knowledge gap, we conducted a large-scale epidemiologic study leveraging RV typing data from over 12,000 infections pooled from 20 studies in the United States, Finland, and Australia. We hypothesized that some RV types are consistently common over time, and that a subset of RV types is more often detected in young children.

METHODS

Data pooling

We pooled RV diagnostic information from 20 studies (4570 children, 12,697 detections) which included PCR and partial sequencing data of 11960 nasal samples of children ages 0-18 years collected from 1997 to 2025.[15] Studies were in broad geographic regions of the United States as well as Finland (30-MAR) and Australia (CAS, MAVRIC). Country-level subanalyses were not performed because detections from non-US countries were limited and insufficient for longitudinal comparison. Ten of the US cohorts are in the National Institutes of Health Environmental Influences on Child Health (ECHO) program: COAST, CCAAPS, CCCEH, URECA, WHEALS, INSPIRE, WISC, MAAP, CANOE, and MARC-35 (see Table E1 in the Online Repository available at www.jacionline.org).[22] Each study obtained participant guardians' informed consent and approval from local ethics review boards. Respiratory specimens were collected both during symptomatic respiratory illnesses and through active surveillance per individual study protocols of mostly healthy children. All samples that tested positive for the presence of RV or enterovirus were sent for downstream sequencing to identify virus species and types. Enterovirus samples were later excluded, as our analysis only focused on RV type–specific circulation. Unless otherwise noted, multiple RV types detected in a sample were counted as separate infections.

RV typing

All samples underwent the same standardized molecular typing workflow based on analysis of partial 5′ untranslated region sequences. For select RV-C types with high sequence identity in the 5′ untranslated region, typing was further confirmed by VP4/VP2 sequence analysis using previously published methods.[23,24] RV types in clinical samples were assigned by sequence identity comparisons with published RV reference sequences, as described elsewhere.[23] The 5′ untranslated region sequence information was lacking for a small subset of novel types (A107, A109, B100, B105, B106, C52) that were officially assigned using partial capsid sequences.[14] Consequently, these types were not included in calculations of relative prevalence.

Analysis of temporal trends in RV prevalence

We displayed RV relative prevalence over time by stream graphs, which were generated by the 'ggstream' package in RStudio (parameters: bw = 0.8, n_grid = 1000). RV types with insufficient typing data were excluded from the stream graph analyses. Mixed effects logistic regression models were used to estimate linear trends by calendar year in RV prevalence for each species, while adjusting for age (using a natural cubic spline with 4 degrees of freedom) as a fixed effect and subject as a random effect. Clusters of RV species (defined as common linear trends) were obtained from the slope estimates and associated standard errors using nonparametric maximum likelihood estimation of a mixture model; empirical Bayes methods were used to assign species to the mixture components.[23,24] Plots were initially generated by the 'ggpubr' package with the GGally and 'ggpmisc' extensions, and were grouped into quartiles for some analyses.

Phylogenetic tree

To understand whether genetic relatedness influences virus circulation patterns, we constructed a phylogenetic tree overlaid with RV type counts in our dataset. The tree was constructed using VP1 gene reference sequences of all sequenced RV-A, RV-B, and RV-C types, with enterovirus sequences included as an outgroup. Sequences were aligned and analyzed in MEGA (Molecular Evolutionary Genetics Analysis)[25] software using the proportional distance model (aka p-distance model), uniform rates, and 500 bootstrap replicates. Bar counts were added using publicly available Iroki software.[26]

Analysis of age-specific RV associations

In our analysis of age trends, infants were defined being aged 0 to <1 year, toddlers 1 to <4 years, school-age children as 5 to <8 years, and adolescents as 9 to 18 years. Spearman correlation coefficients were calculated to compare RV type prevalence pairwise across age brackets and were visualized as correlation matrices by the 'ggcorrplot' package. We defined a significance value of $\alpha = .05$. To evaluate whether changes in participant age over time could bias temporal patterns in virus circulation, we assessed the relationship between age at collection and calendar year using the full RV-C dataset. Among 5624 RV-C–positive samples, age showed only a minimal correlation with year (Pearson $r = 0.17$; 95% confidence interval [CI], 0.144, 0.196; Spearman $\rho = 0.077$), accounting for 2.9% of variance ($r^2 = 0.029$) with no meaningful collinearity (variation inflation factor ≈ 1.03). Similar results were observed for RV-A (Pearson $r = 0.21$, $P = 1.3 \times 10^{-54}$; Spearman $\rho = 0.116$, $P = 2.0 \times 10^{-18}$; variation inflation factor ≈ 1.04) and RV-B (Pearson $r = 0.24$, $P = 2.0 \times 10^{-23}$; Spearman $\rho = 0.144$, $P = 2.8 \times 10^{-9}$; variation inflation factor ≈ 1.06), with all correlations explaining only a small proportion of variance. Together, these findings indicate that participant age remained stable across the study period for all RV species and therefore is unlikely to confound temporal analyses. The small increase over time can be explained by the presence of multiple birth cohorts.

CDHR3 rs6967330 genotype associations

For study participants with known *CDHR3* rs6967330 genotype, we compared the proportion of RV-C detections in individuals with the risk genotypes AA or AG to those with the GG wild-type genotype. The strength of linearity was assessed by Pearson correlation, again with an alpha of .05. The underlying code for this work is available in GitHub.

RESULTS

Study population

We compiled 20 pediatric studies between 1997 and 2025, with virus diagnostics that included RV typing (Table I and Fig 1). The studies included birth cohorts, randomized controlled trials and case–cohort studies of children from whom specimens were collected during periods of illness and surveillance samples from mostly healthy children. These studies analyzed nasal samples using similar RV diagnostics that included real-time reverse transcriptase PCR and partial sequencing to determine virus type. A total of 12,697 RV isolates were detected and typed in 11,960 nasal samples. Participants ranged in age from 0 to 18 years, with a median age of 3.4 years at the time of sampling, and just over half were boys. The study population from the United States, Finland, and Australia was geographically and racially diverse (self- or family-identified White 61%, Black or African American 20%). *CDHR3* rs6967330 genotypes were known for 50% of the study population.

Circulation patterns over time

Among the 11,960 nasal samples, the frequency of detection for individual RV types varied from 0 to 286 (2.4%) (see Figs E1 and E2 in the Online Repository available at www.jacionline.org). There was similar variability among RV-A, RV-B, and RV-C. Stream graphs illustrate long-term circulation patterns for RV types, particularly RV-A and RV-C, which show consistent visual trends across the study period. When types were grouped into quartiles by frequency of detection within species (Fig 2, *A-C*), the top quartiles of RV-A, RV-B, and RV-C comprised nearly half of all viruses detected, while the bottom quartiles were generally <10% of viruses detected. Quartiles of relative RV type frequency within each species appeared similar throughout the 27-year study period (Fig 2, *A-C*). Within the high-prevalence quartiles, the predominant types for each species also showed recurring patterns over time (Fig 2, *D-F*).

As a quantitative measure of circulation stability over time, we estimated the slope of detection frequency over the study period for each RV type, adjusting for age and random effect of subject within the studies. The 95% CIs of the slopes included zero for 147 (97%) of 151 of types with sufficient data. In addition, we performed a cluster analysis of the slopes for each species to determine whether certain subgroups exhibited different circulation patterns. All RV-A types clustered together, except RV-A15 (Fig 3, *A*). All RV-B types also clustered together (Fig 3, *B*), as did all RV-C types (Fig 3, *C*).

TABLE I. Demographic summary of pediatric participants included in RV longitudinal analysis

Variable	Value	Recorded data	Missing data
Study population			
No. of participants	4570		
RV detected*	12,697		
Age (years)		12,697 (100)	0
Mean [SD]	4.8 [4.4]		
Median	3.4		
Age range			
Infant (0 to <1 years)	2963 (23.3)		
Toddler (1 to <3 years)	2955 (23.3)		
School age (3 to <12 years)	5738 (45.2)		
Adolescent (12 to 18 years)	1041 (8.2)		
Sex		12,697 (100)	0
Female	5482 (43.2)		
Male	7215 (56.8)		
Race		12,696 (100)	1 (0)
White	7752 (61.1)		
Black or African American	2589 (20.4)		
Hispanic	1313 (10.3)		
Other	420 (3.3)		
Multirace	588 (4.6)		
Not available	34 (0.3)		
CDHR3 rs6967330 genotype		5996 (47.2)	6701 (52.8)
AA	287 (4.8)		
AG	1999 (33.3)		
GG	3710 (61.9)		

Data are presented as nos. (%) unless otherwise indicated.
SD, Standard deviation.
*In 11,960 nasal samples where at least one RV was detected.

Detection frequency and phylogenetic relationships

We compared RV type detection frequency with phylogenetic similarity of VP1 sequences, which encode the most variable and immunogenic capsid protein, to evaluate whether virus genetics influenced relative frequency. Overall, both common and rare RV types were broadly distributed across the phylogenetic tree (Fig 4). Only a few of the most common types clustered together (eg, A12 and A78, C2 and C40).

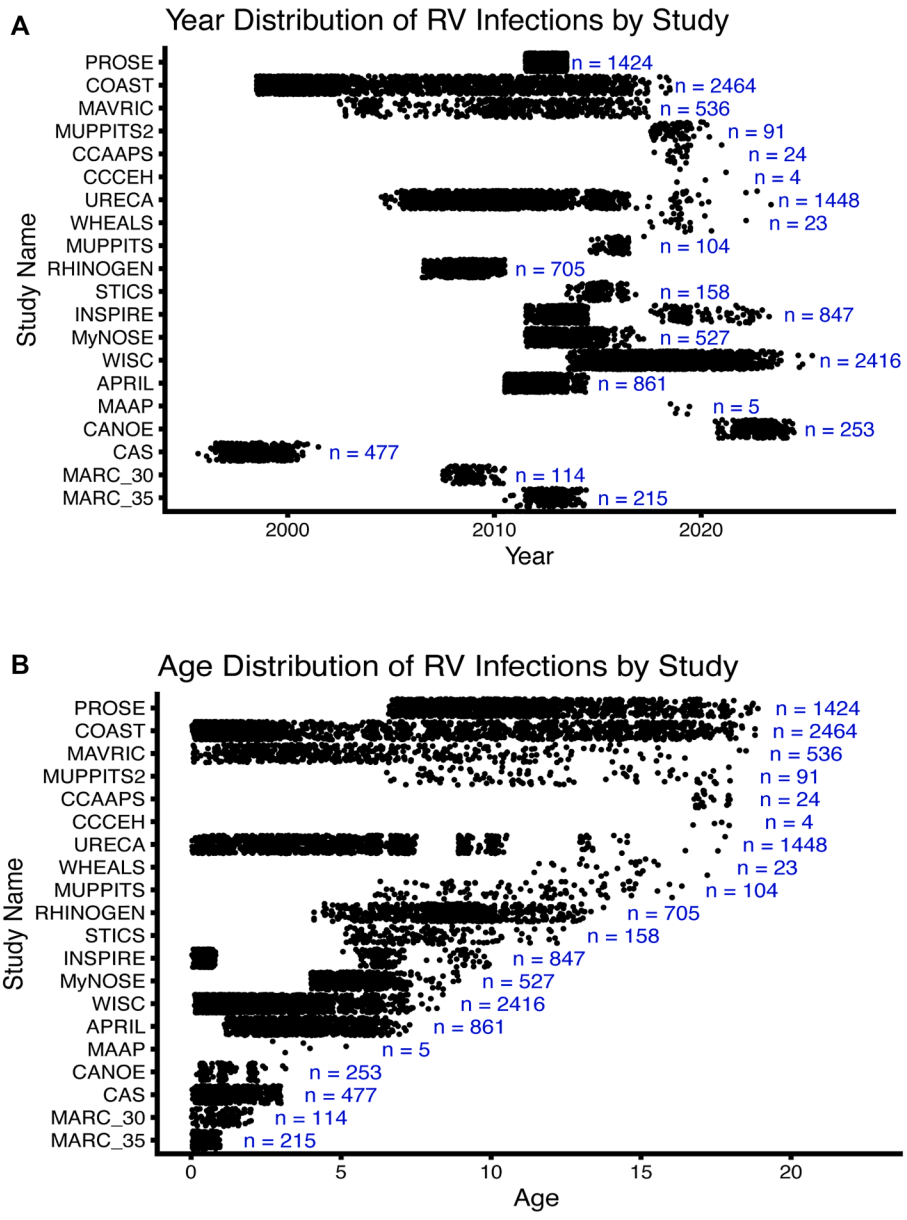

FIG 1. Multistudy analysis of RV detection with age distribution and sample collection timeline. Jitter plots visualize age distribution of clinical RV detections by study **(A)** and calendar year **(B)**. Each *dot* represents 1 detection; study acronyms are grouped along y-axis. Associated numbers of RV detections for each study are indicated.

Age-specific distribution of RV types

We next analyzed distribution patterns of the most commonly detected RV types within each species for different pediatric age brackets, including infants, toddlers, school-age children, and adolescents (Fig 5, *A-C*). Age was related to distinct infection patterns that progressively changed across the age brackets. Common types such as RV-A78, RV-B52, and RV-C2 were most frequently detected in infants but were not among the most frequent types in older children. In contrast, a few types (eg, A101, B6, C11) were common in all pediatric age groups.

To compare RV type distribution between different age groups, we performed Spearman rank correlations using relative frequencies of types among age groups (Fig 5, *D-F*). Common RV types showed strong or moderate correlations between adjacent age groups, with weaker correlations observed between more distant age groups.

CDHR3 genetics and RV-C types

We next tested whether *CDHR3* rs6967330 risk genotypes, which are associated with increased risk for RV-C infection and wheezing illnesses,[18,27] increased the relative risk of infection with less common RV-C types. Among the 5996 RV positive samples with available host genotypes, the relative detection frequency of RV-C types was similar between those with AA/AG risk genotypes and those with the GG wild-type genotype

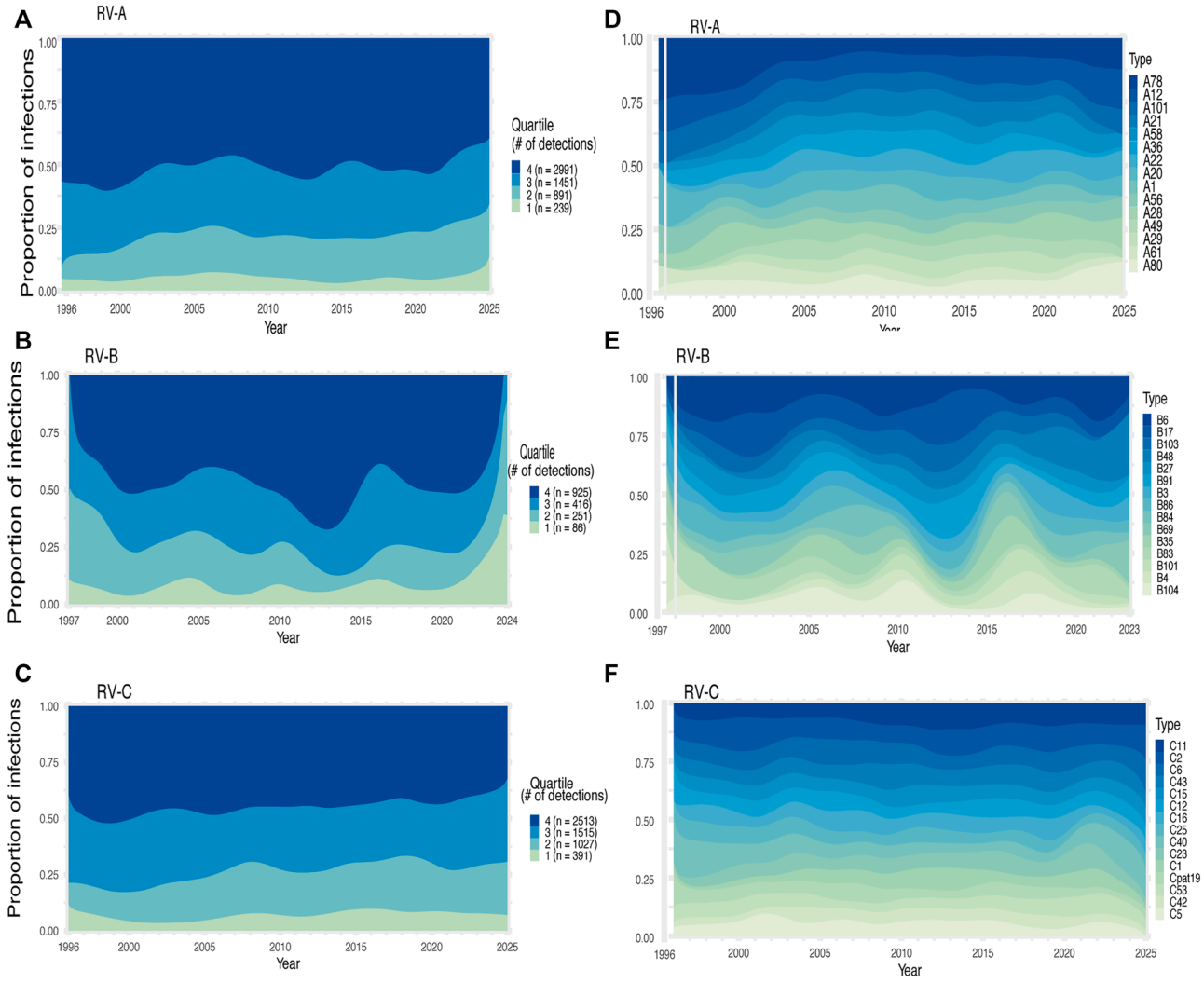

FIG 2. Temporal dynamics and prevalence of RV-A, RV-B, and RV-C types in clinical studies from 1997 to 2025. Quartile stream graphs summarize overall distribution of all detected RV types over study period for each species: **(A)** RV-A, **(B)** RV-B, and **(C)** RV-C. Each stream represents quartile of RV types ranked by detection frequency from most to least common. Stream graphs **(D-F)** display relative abundance of top 15 RV types within each species, where each stream represents distinct type.

(Pearson coefficient $r = 0.89$; 95% CI, 0.83, 0.93; see Fig E3 in the Online Repository available at www.jacionline.org). This relationship was similar in strength to those for RV-A ($r = 0.86$; 95% CI, 0.79, 0.91) and RV-B ($r = 0.87$; 95% CI, 0.72, 0.94).

DISCUSSION

RVs are the most common respiratory viruses circulating in the community and contribute significantly to the burden of lower respiratory illnesses, particularly in individuals with asthma. The remarkable genetic diversity of RV and large number of types are significant obstacles to developing therapeutic or preventive treatments. We hypothesized that there is a subset of more common RV types with stable circulation patterns. These viruses may represent a focus for development of therapeutics toward RV.

We addressed this hypothesis in a large multinational pooled dataset with diversity in geographic distribution, age, race, and *CDHR3* genotype. The results show remarkable temporal stability of RV type prevalence, with consistent detection of common and rare types. Age-specific infection patterns revealed strong correlations between adjacent age groups, as measured by Spearman correlation coefficients (ρ), with correlations becoming weaker when comparing age groups that were further apart. Phylogenetic analysis showed that both common and rare types were broadly distributed across the tree, with only limited evidence that genetic relatedness influenced their relative prevalence.

Other studies have reported that some RV types appear to be more common.[28-31] For example, a recent meta-analysis of 31 studies conducted across Asia, Europe, and Africa identified a set of common RV types that overlaps those reported here.[21] Our study extends these previous findings with a time trend analysis demonstrating remarkable RV type circulation stability over a 27-year period. Types that were common in the late 1990s remain prevalent, while rare types continue to be infrequently detected. This pattern stands in stark contrast to other respiratory viruses

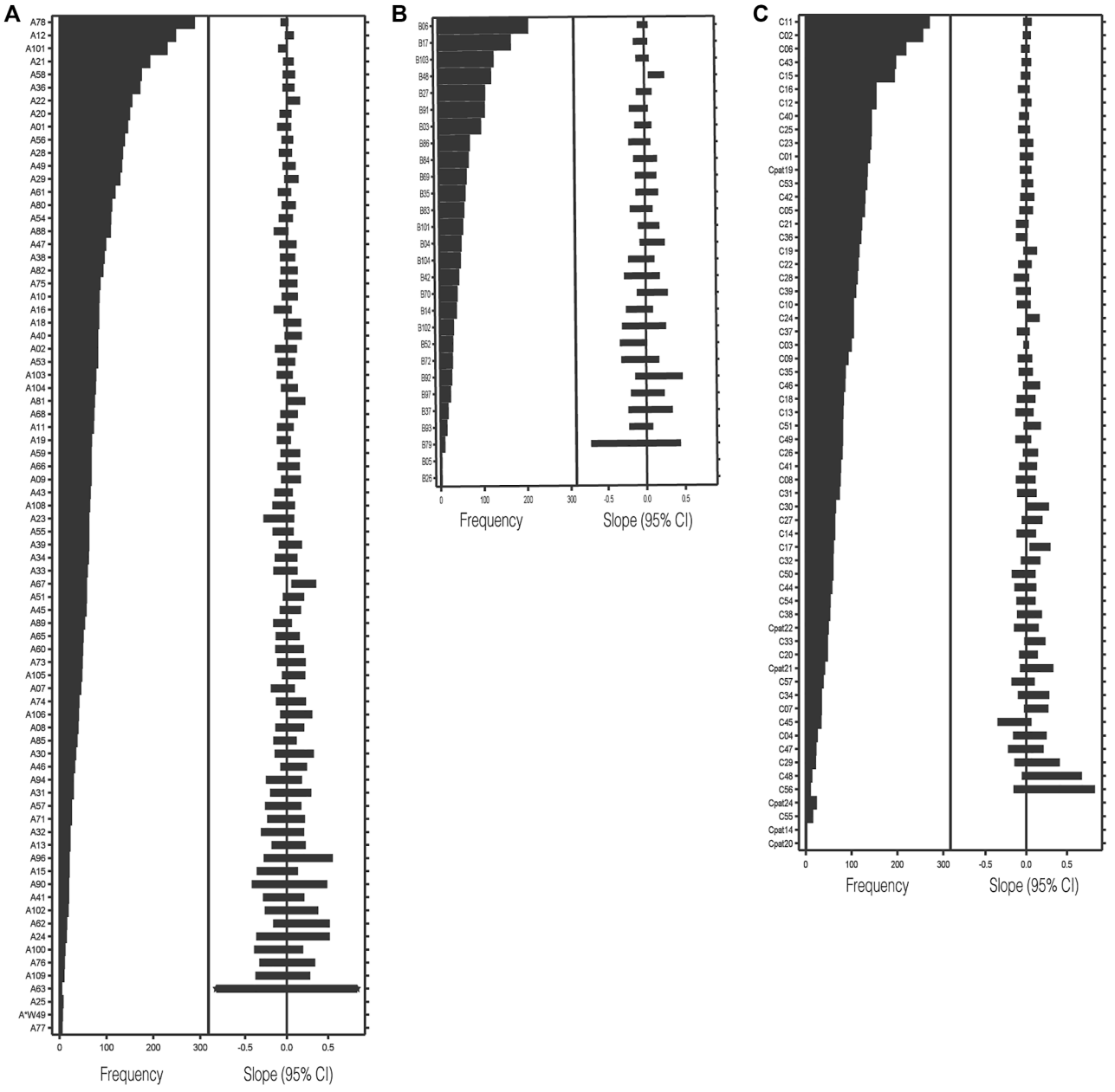

FIG 3. Stability of RV detection over study period. Estimated slope of RV detection over study period for each type by species: **(A)** RV-A, **(B)** RV-B, and **(C)** RV-C. Cluster analysis showed stable circulation throughout study period.

such as influenza A/B and severe acute respiratory syndrome coronavirus 2, which shows a population structure characterized by periodic replacement of strains with increased relative fitness and limited long-term cocirculation.[14] In contrast, RV exhibits extensive cocirculation and broad strain diversity, likely maintained through high mutation rates,[32] recombination,[33] limited cross-immunity,[12] and the absence of strong transmission bottlenecks.[34]

The factors that distinguish common from rare RV types are unknown. The prevalence of certain RV types could be driven by variations in capsid stability, receptor binding affinity, or replication efficiency (ie, inherent differences in basic reproduction number, or R_0). Alternatively, there could be more complex immune interactions at play that allow for common viruses to suppress circulation of less common types (comparable R_0 but occupying similar ecological or immunologic niche). These potential mechanisms are currently under investigation. Age-related patterns in RV infection were also evident. While previous work has demonstrated species-level differences (eg, RV-A is more common in older children and RV-C in younger children), our data indicate that age is also associated with RV type. Many of the most common RV types (eg, RV-A78, RV-C2) were more prevalent in infants and toddlers. These findings suggest that infants and toddlers, who efficiently spread the virus,[35] could be infected with these common types and then develop long-lasting immunity that protects them against reinfection. However, there were a few common types (eg, RV-A101, RV-C11) that were

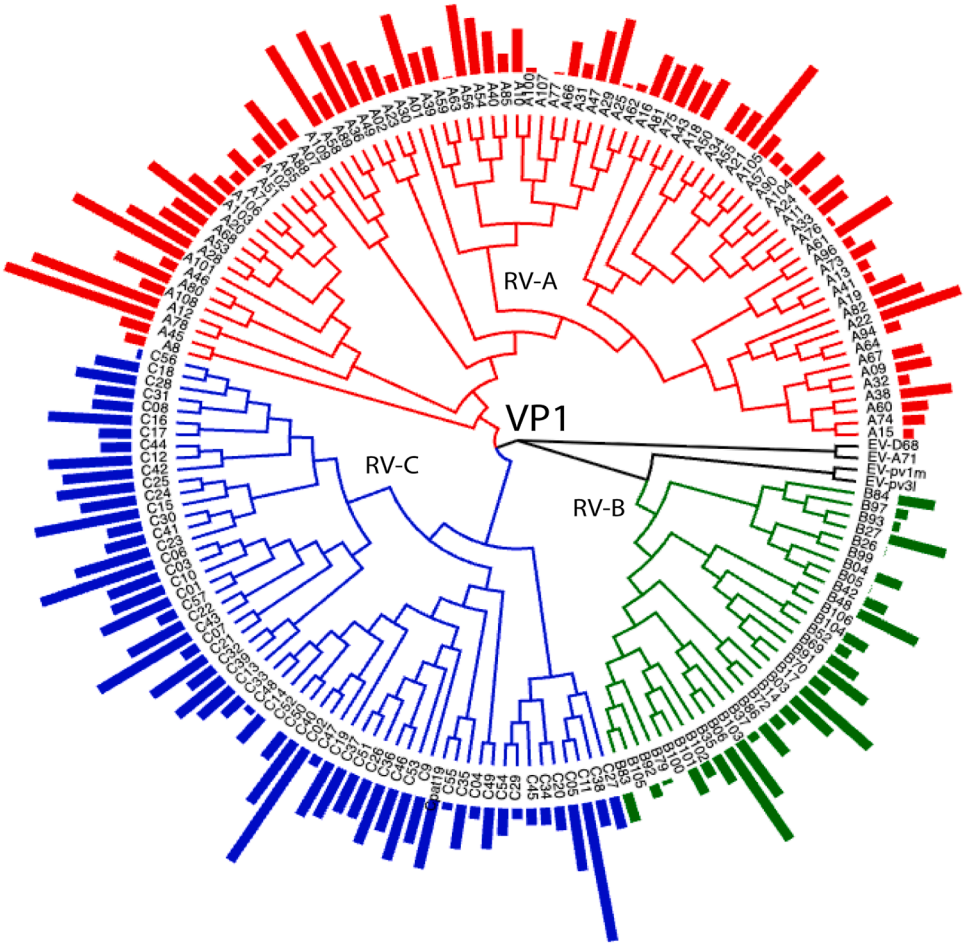

FIG 4. Phylogenetic tree of RV-A, RV-B, and RV-C types with their detection frequency. Phylogenetic tree was constructed using VP1 gene reference sequences with RV-A *(red),* RV-B *(green),* and RV-C *(blue)* detections overlaid. Nucleotide sequences were aligned and analyzed by MEGA using proportional distance (p-distance) model, uniform rates, and 500 bootstrap replicates. Bar heights represent number of detections of each RV type in our dataset.

highly prevalent across all age groups. Further studies are needed to identify the features that distinguish common from rare viruses. Identifying which RV types most commonly affect infants and young children, who are most likely to be hospitalized with RV infections, is an essential goal for targeted interventions.

The top 15 circulating RV-A and RV-C types accounted for approximately 50% of all detections. The extraordinary genetic diversity of RV, with over 160 recognized types, has long been a major barrier to vaccine and antiviral development. If interventions must be type specific, identifying which types dominate circulation and disproportionately affect high-risk age groups becomes critical. Our findings address this gap by demonstrating that a smaller subset of RV-A and RV-C types account for approximately 50% of all detections and remain stable over decades. This stability suggests that therapeutic programs could focus on these consistently prevalent types rather than attempting to cover the entire RV diversity. Moreover, age-specific patterns highlight types that are most common in infants and toddlers—the population with the highest burden of severe RV illness—thus providing actionable targets for early-life prophylaxis or treatment strategies. These insights offer a practical road map for prioritizing targets in vaccine and antiviral development programs. Even with narrowing the number of targets, vaccine development would remain challenging given limited cross-neutralization.[12] Vaccine approaches could include highly multiplexed vaccines[36] or those that promote broad efficacy by eliciting responses to shared T-cell epitopes.[37]

Our dataset spans the severe acute respiratory syndrome coronavirus 2 pandemic period,[38] during which many common respiratory viruses experienced marked declines and shifts in circulation trends. One of the most striking examples is the complete disappearance of the influenza B/Yamagata lineage, which became extinct during the widespread social distancing measures.[39] In contrast, RV circulation was minimally affected.[1] Our data provide additional evidence that type-specific RV circulation remained largely stable throughout the pandemic years.

We also explored the role of host genetics, specifically the *CDHR3* rs6967330-A risk allele, which increases epithelial surface expression of the RV-C receptor.[40,41] While this allele was associated with an overall increase in RV-C infection frequency, it did not preferentially increase the detection of rare RV-C types.

Strengths of our study include a large and racially diverse pediatric population with broad geographic representation across the United States, Finland, and Australia. The use of standardized

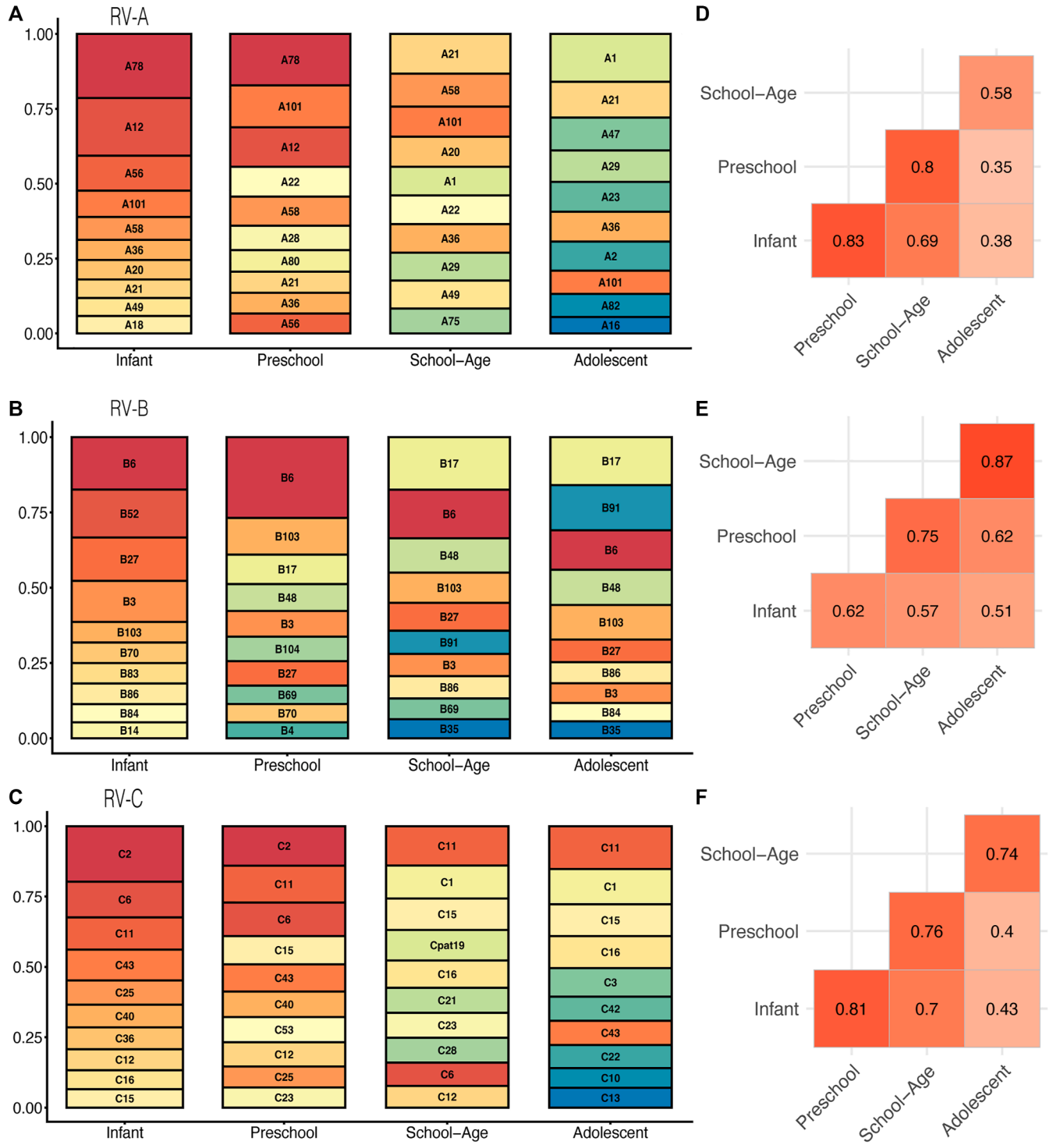

FIG 5. RV infection across pediatric age groups. Ten most common RV types are shown for each species—**(A)** RV-A, **(B)** RV-B, and **(C)** RV-C—stratified by age categories: infant (0 to <1 year), toddler (1 to 4 years), school age (5 to <8 years), and adolescent (9 to 17 years). Each *color* represents distinct RV type, with *new colors* indicating types that emerge as common in older age groups. **(D-F)** Spearman correlation coefficient matrices illustrate strength of pairwise association in RV type prevalence between age groups. Correlation coefficients were calculated using relative frequencies of RV types within each species. All $P < .05$ for RV-A, RV-B, and RV-C.

and highly sensitive viral diagnostics (2-step real-time reverse transcriptase PCR and sequencing) across all studies ensures consistency in RV detection and typing. Longitudinal sampling from birth cohorts enhances internal validity, while the 27-year time span offers a rare opportunity to assess RV circulation stability over time. Limitations of our analysis include the

heterogeneity across the included studies, which precluded calculation of actual prevalence rates for RV species and types. Instead, we the calculated relative detection frequency of RV types. Our pooled dataset includes studies with heterogeneous designs, which may limit the generalizability of the findings to the broader pediatric population. Because these designs include birth cohorts, longitudinal cohorts, randomized controlled trials, and case–control studies with varying inclusion criteria, some degree of selection and information bias is unavoidable. Our findings should be interpreted in the context of this heterogenous collection of studies rather than longitudinal surveillance. However, our dataset included cohort studies that sampled the same individuals longitudinally over more than 10 years, and sensitivity analyses within these studies confirmed the primary findings (see Fig E5 in the Online Repository available at www.jacionline.org). Additionally, the absence of adult data limits generalizability to older populations. There also known limitations when using stream graph visualization to monitor virus circulation. Stream graphs require smoothing and interpolation, which may obscure sharp year-to-year variation; thus, the visualization should be interpreted as a qualitative summary of long-term patterns rather than a precise representation of annual counts.

In conclusion, our study highlights the remarkable long-term stability of common and rare RV types in circulation and identifies some viruses that are more common in infants and preschoolers. These findings carry important public health implications. RV circulation patterns differ markedly from many other virus species, with little evidence of disruption by host immune pressure. The sustained high prevalence of some types identifies critical targets for RV vaccines and antivirals. Therapeutic development programs should therefore prioritize coverage of these common types, and particularly those frequently causing illnesses in young children, who have the highest burden of RV-induced lower respiratory tract illnesses.

DISCLOSURE STATEMENT

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Data availability statement: Select deidentified data from the ECHO Program are available through the Eunice Kennedy Shriver National Institute of Child Health and Human Development's Data and Specimen Hub (DASH). A deidentified dataset of all data used as part of these analyses can be made available on request for any proposed analysis.

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Key messages

- **RV type circulation has remained remarkably stable over 3 decades, with most types showing no significant change in detection frequency.**
- **Commonly detected RV types do not cluster phylogenetically, indicating that capsid sequence similarity does not fully explain type-level fitness.**
- **Certain RV types are consistently prevalent across all pediatric age groups, while others disproportionately affect younger children.**
- **The *CDHR3* rs6967330-A risk allele increases overall RV-C infection rates but does not alter the distribution of common versus rare RV-C types.**

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