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The role of viral interaction in household transmission of symptomatic influenza and respiratory syncytial virus

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The role of viral interaction—where one virus enhances or inhibits infection with another virus—in respiratory virus transmission is not well characterized. This study used data from 4029 total participants from 957 households who participated in a prospective household cohort study in Southeast Michigan, U.S.A to examine how viral coinfection and cocirculation may impact transmission of symptomatic influenza and respiratory syncytial virus infections. We utilized multivariable mixed effects regression to estimate transmission risk when index cases were coinfected with multiple viruses and when viruses cocirculated within households. This analysis included 201 coinfections involving influenza A virus, 67 involving influenza B virus, and 181 involving respiratory syncytial virus. We show that exposure to symptomatic coinfected index cases was associated with reduced risk of influenza A virus and respiratory syncytial virus transmission compared to exposure to singly infected cases, while infection with another virus was associated with increased risk of acquisition of these viruses. Exposure to coinfected cases among contacts infected with other viruses was associated with increased risk of influenza B virus acquisition. These results suggest that viral interaction may impact symptomatic transmission of these viruses.

Acute respiratory infections (ARIs) are a major cause of morbidity and mortality worldwide[1,2]. In the United States, influenza viruses and respiratory syncytial virus (RSV) contribute to substantial societal and economic burden[3,4], especially impacting young children, adults aged 65+ years, and individuals with underlying conditions[5]. Understanding factors that impact the transmission of these respiratory viruses is crucial for estimating population risk and developing public health prevention strategies.

Household studies of respiratory virus transmission often focus on the transmission of a single virus but may not account for the possibility of cocirculation of multiple viruses simultaneously within a household. Respiratory viruses frequently cocirculate in communities[6] and coinfect individuals[7]. When multiple respiratory viruses are introduced into a household, interaction between these viruses could occur, and such interaction may or may not affect transmission. The possibility of virus–virus interaction, a phenomenon where circulation of one virus enhances or inhibits infection with a second virus, has long been speculated based on population-level patterns. Theoretically, viruses may interact with each other positively, exhibiting synergism, or negatively/antagonistically[8]. The exact mechanisms of interaction

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that may exist at the individual level are not fully understood, nor are the implications of virus–virus interaction for transmission. Specifically, there is a paucity of data regarding viral transmission in the presence of more than one virus within a household—for example, whether viruses are more or less likely to transmit when an index case is coinfected or when a household contact is infected with a different virus. One study[9] identified coinfection among index cases as a risk factor for virus transmission. Another study[10] observed increased susceptibility to infection with influenza during or immediately following infection with RSV. Notably, some viruses have been shown to have different viral loads when coinfecting with other viruses compared to infecting on their own[11,12]. Whether such impacts on viral load through viral interference affect transmission is unclear.

Here we examine the possible impacts of viral interaction on transmission of influenza A virus (IAV), influenza B virus (IBV), and RSV within households. We used data from the Household Influenza Vaccine Evaluation (HIVE) study—a prospective cohort study in Michigan—from the years 2010 to 2020 to assess the relationship between the cocirculation of multiple viruses within a household and transmission to exposed household members. We show that exposure to symptomatic coinfected index cases was associated with a reduced risk of IAV and RSV transmission compared to exposure to singly infected index cases, while infection with another virus was associated with an increased risk of acquisition of IAV and RSV; exposure to coinfected cases among contacts infected with other viruses was associated with increased risk of IBV acquisition. Our results suggest that viral interaction may impact the transmission of influenza viruses and RSV within households.

Results

Study population

From October 2010 through June 2020, 957 households participated in the HIVE study, with 4029 total participants. During this time, 546 household clusters involved IAV, with 786 total cases; 231 clusters involved IBV, with 301 total cases; 370 clusters involved RSV, with 493 total cases (Table 1). There were no influenza or RSV illnesses identified in the study population from March 2020 through the end of that study year, which was June 30, 2020. The sex of index cases, secondary cases, and uninfected contacts generally followed the pattern of the larger HIVE cohort (51.6% female vs. 48.4% male) except IAV, in which males (56.1%) represented a greater proportion of secondary cases than females (Tables 2–4). For IAV, the age groups that made up the highest proportion of index cases were ages 6–11 (30.1%) and 18–49 (30.7%); the largest proportion of secondary cases were in the 18–49 age group (36.8%), which aligns with the distribution of the overall HIVE cohort (39.0%). For IBV, the highest proportion of index cases were in the 6–11 age group (40.9%), while the highest proportion of secondary cases were in the 0–5 age group (37.2%), which is greater than the proportion of the overall HIVE cohort comprised of ages 0–5 (25.3%). For RSV, the highest proportion of index (49.4%) and secondary (41.7%) cases were in the 0–5 age group. For all three viruses of interest, over 60% of index cases,

Table 1 | Characteristics of household illness events by primary virus of interest

Characteristic	Influenza A virus	Influenza B virus	Respiratory syncytial virus
Household illness events, no.	546	231	370
Mean (range) illness events per household	1.6 (1–7)	1.3 (1–4)	1.4 (1–6)
Mean (range) no. household members	5 (3–9)	5 (3–9)	5 (3–10)
Mean (range) serial interval in days	3.6 (1–18)	4.0 (1–18)	4.5 (1–14)
Mean (range) days from symptom onset to specimen collection of cases	2.5 (0–10)	2.6 (0–9)	2.8 (0–9)
Coinfected	2.5 (0–7)	2.7 (0–8)	2.9 (0–8)
Singly infected	2.6 (0–10)	2.6 (0–9)	2.8 (0–9)
Cases, no.	786	301	493
Index, no. (%)	574 (73.0%)	242 (80.4%)	385 (78.1%)
Secondary, no. (%)[a]	212 (27.0%)	59 (19.6%)	108 (21.9%)

[a]The proportion of secondary cases that made up the total case count for each virus was compared using Pearson's Chi-squared test for homogeneity. Proportions were significantly different across viruses ($P = 0.02$).

Table 2 | Characteristics of HIVE study participants involved in influenza A virus household illness events from 2010 to 2020

Characteristic		Index cases	Secondary cases	Uninfected contacts	HIVE study[a]
Sex, *n* (%)	F	289 (50.4%)	93 (43.9%)	811 (51.5%)	2078 (51.6%)
	M	285 (49.7%)	119 (56.1%)	765 (48.5%)	1951 (48.4%)
Age Group, *n* (%)	0–5	130 (22.7%)	53 (25.0%)	266 (16.9%)	1035 (25.7%)
	6–11	173 (30.1%)	47 (22.2%)	380 (24.1%)	759 (18.8%)
	12–17	75 (13.1%)	25 (11.8%)	232 (14.7%)	410 (10.2%)
	18–49	176 (30.7%)	78 (36.8%)	635 (40.3%)	1463 (36.3%)
	50+	20 (3.5%)	9 (4.3%)	63 (4.0%)	115 (2.9%)
Influenza Vaccination, *n* (%)	No	154 (31.2%)	59 (32.2%)	426 (32.1%)	1154 (28.6%)
	Yes	340 (68.8%)	124 (67.8%)	902 (67.9%)	2202 (54.7%)
	Missing	80	29	248	673
Coinfected, *n* (%)	No	416 (72.5%)	169 (79.7%)	1555 (98.7%)	–
	Yes	158 (27.5%)	43 (20.3%)	21 (1.3%)[b]	

Participants may have appeared multiple times as index or secondary cases or uninfected contacts if involved in more than one household illness event.
[a]Characteristics of Household Influenza Vaccine Evaluation (HIVE) study participants, including sex, age group at the time of initial enrollment, and influenza vaccination status for that year.
[b]Coinfected with non-influenza A viruses.

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Table 3 | Characteristics of HIVE study participants involved in influenza B virus household illness events from 2010 to 2020

Characteristic		Index cases	Secondary cases	Uninfected contacts	HIVE study[a]
Sex, *n* (%)	F	117 (48.3%)	31 (52.5%)	362 (50.8%)	2078 (51.6%)
	M	125 (51.7%)	28 (46.5%)	351 (49.2%)	1951 (48.4%)
Age Group, *n* (%)	0–5	56 (23.1%)	22 (37.2%)	92 (12.9%)	1035 (25.7%)
	6–11	99 (40.9%)	15 (25.4%)	164 (23.0%)	759 (18.8%)
	12–17	38 (15.7%)	4 (6.8%)	109 (15.3%)	410 (10.2%)
	18–49	44 (18.2%)	17 (28.8%)	317 (44.5%)	1463 (36.3%)
	50+	5 (2.1%)	1 (1.7%)	31 (4.4%)	115 (2.9%)
Influenza Vaccination, *n* (%)	No	76 (36.5%)	15 (30.6%)	221 (36.0%)	1154 (28.6%)
	Yes	132 (63.5%)	34 (69.4%)	393 (64.0%)	2202 (54.7%)
	Missing	34	10	99	673
Coinfected, *n* (%)	No	186 (76.9%)	48 (81.4%)	711 (99.7%)	–
	Yes	56 (23.1%)	11 (18.6%)	2 (0.3%)[b]	

Participants may have appeared multiple times as index or secondary cases or uninfected contacts if involved in more than one household illness event.
[a]Characteristics of Household Influenza Vaccine Evaluation (HIVE) study participants, including sex, age group at the time of initial enrollment, and influenza vaccination status for that year.
[b]Coinfected with non-influenza B viruses.

Table 4 | Characteristics of HIVE study participants involved in respiratory syncytial virus household illness events from 2010 to 2020

Characteristic		Index cases	Secondary cases	Uninfected contacts	HIVE study[a]
Sex, *n* (%)	F	203 (52.7%)	61 (56.5%)	584 (50.9%)	2078 (51.6%)
	M	182 (47.3%)	47 (43.5%)	564 (49.1%)	1951 (48.4%)
Age Group, *n* (%)	0–5	190 (49.4%)	45 (41.7%)	185 (16.1%)	1035 (25.7%)
	6–11	82 (21.3%)	23 (21.3%)	256 (22.3%)	759 (18.8%)
	12–17	34 (8.8%)	6 (5.6%)	134 (11.7%)	410 (10.2%)
	18–49	70 (18.2%)	31 (28.7%)	534 (46.5%)	1463 (36.3%)
	50+	9 (2.3%)	3 (2.8%)	39 (3.4%)	115 (2.9%)
Influenza Vaccination, *n* (%)	No	89 (25.8%)	27 (24.5%)	278 (27.9%)	1154 (28.6%)
	Yes	256 (74.2%)	79 (74.5%)	717 (72.1%)	2202 (54.7%)
	Missing	40	2	153	673
Coinfected, *n* (%)	No	235 (61.0%)	77 (71.3%)	1130 (98.4%)	–
	Yes	150 (39.0%)	31 (28.7%)	18 (1.6%)[b]	

Participants may have appeared multiple times as index or secondary cases or uninfected contacts if involved in more than one household illness event.
[a]Characteristics of Household Influenza Vaccine Evaluation (HIVE) study participants, including sex, age group at the time of initial enrollment, and influenza vaccination status for that year.
[b]Coinfected with non-respiratory syncytial virus (RSV) viruses.

secondary cases, and non-cases received the seasonal influenza vaccine.

Household transmission

The proportion of secondary cases was significantly different ($P = 0.02$) for IAV (27.0%), IBV (19.6%), and RSV (21.9%). The proportion of coinfected cases was significantly different ($P < 0.001$) across viruses; for RSV, 39.0% of index cases and 28.7% of secondary cases were coinfected, compared to IAV (27.5% of index, 20.3% of secondary) and IBV (23.1% of index, 18.6% of secondary). Of IAV index/secondary case pairs, 80.6% (171/212) corresponded to serial intervals ≤5 days, compared to 76.3% (45/59) of IBV pairs and 66.7% (72/108) of RSV pairs (Fig. 1). The two most identified coinfecting and cocirculating viruses were rhinovirus/enterovirus (RV/EV) and human coronaviruses (HCoV) (Fig. 2).

Household-level analyses

At the household level, the presence of a coinfected index case in the household was associated with a lower risk of transmission to additional household members for IAV (IRR 0.44; 95% CI 0.29–0.66, $P < 0.001$) and RSV (IRR 0.51; 95% CI 0.30–0.86, $P = 0.01$) (Table 5); this association was not significant for IBV (IRR 0.85; 95% CI 0.39–1.84, $P = 0.67$). Having an index case <18 years of age was associated with a greater risk of transmission for IAV (IRR 2.13; 95% CI 1.46–3.10, $P < 0.001$), but was not significant for IBV or RSV. There was no significant association between the number of household members and the risk of transmission for any virus.

Individual-level analyses

At the individual level, exposure to a coinfected index case was associated with reduced acquisition of IAV (OR 0.39; 95% CI 0.23–0.64, $P < 0.001$) and RSV (OR 0.28; 95% CI 0.13–0.60, $P = 0.001$) (Table 6), but was not significant for IBV (OR 0.56; 95% CI 0.20–1.56, $P = 0.27$). Infection with another virus among household contacts was associated with an increase in acquisition of IAV (OR 3.49; 95% CI 2.02–6.03, $P < 0.001$) and RSV (OR 6.05; 95% CI 2.55–14.35, $P < 0.001$) and was not significant for IBV (OR 2.16; 95% CI 0.59–7.96, $P = 0.25$). Exposure to a coinfected index case among contacts infected with a different virus was associated with an increased acquisition of IBV (OR 5.39; 95% CI 1.36–21.37, $P = 0.016$), but this association was not significant for IAV (OR 1.33; 95% CI 0.64–2.75, $P = 0.45$) or RSV (OR 2.29; 95% CI 0.93–5.68, $P = 0.07$). Male sex was significantly positively associated with IAV acquisition (OR 1.40; 95% CI 1.01–1.93, $P = 0.043$), but not IBV or RSV. Exposure to an index case <18 years of age was significantly positively associated with acquisition of IAV (OR 2.58; 95% CI 1.70–3.93, $P < 0.001$) but not the other viruses. Contacts under 5 years of age were

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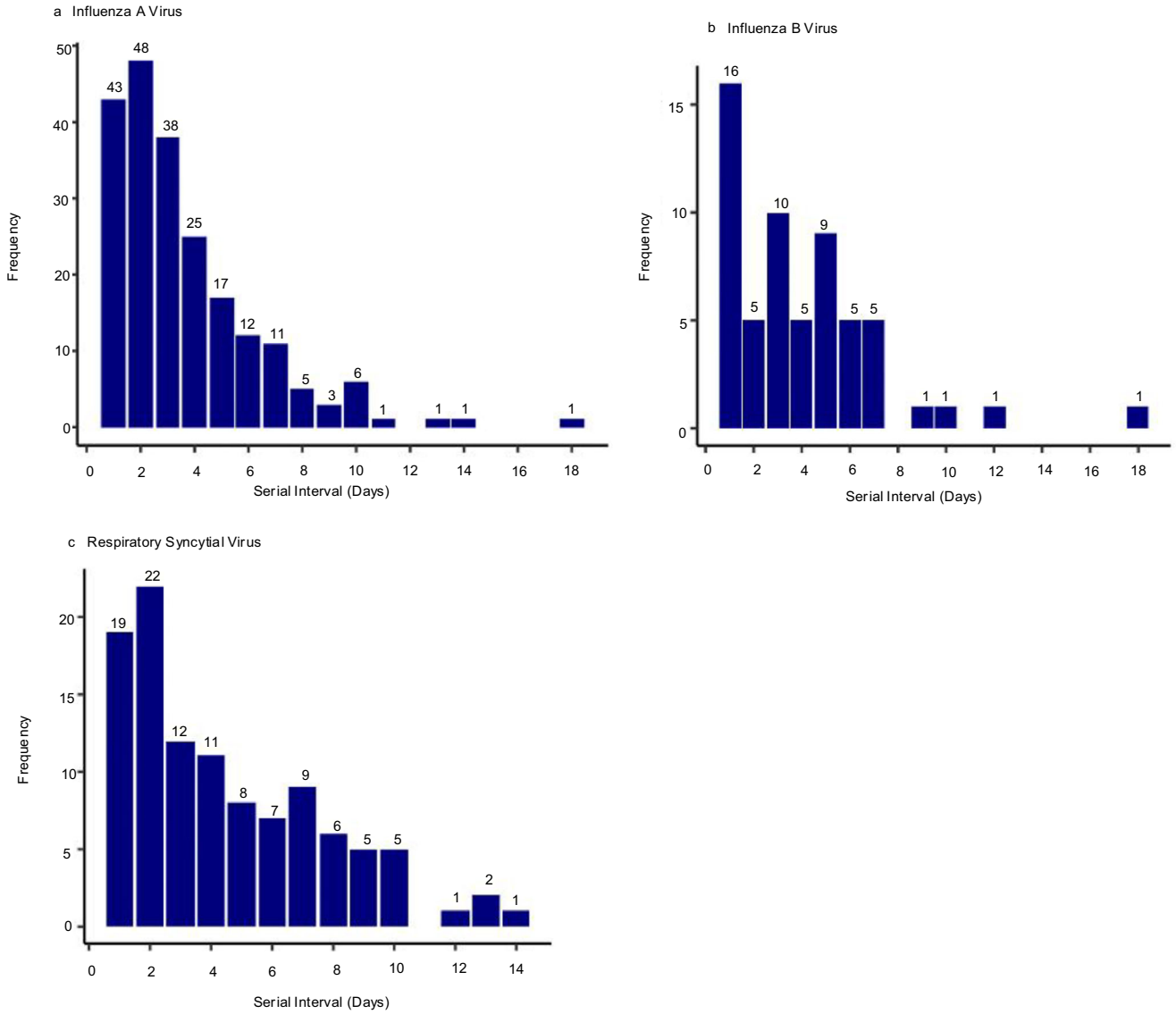

Fig. 1 | Bar plots displaying frequencies of serial intervals for secondary cases involved in household illness events, by virus of interest. a Influenza A virus illness clusters. **b** Influenza B virus illness clusters. **c** Respiratory syncytial virus illness clusters.

more at risk for the acquisition of all viruses of interest. Receipt of the seasonal influenza vaccine ≥14 days prior to household exposure was associated with an increase in acquisition of RSV (OR 2.06; 95% CI 1.11–3.81, $P = 0.021$); there was no significant association for IAV or IBV.

Sensitivity analyses

Changing the transmission timeframe from 1 to 14 days following the index case's illness onset to 2–14 days resulted in 43 IAV cases, 16 IBV cases, and 19 RSV cases being reclassified from secondary to index; this did not substantially impact the direction or magnitude of the effect estimates (Supplementary Table 1). Similarly, the inclusion of cycle threshold (Ct) value for viruses of interest among index cases did not change the direction or magnitude of association (Supplementary Table 2). However, there were significant differences in the distribution of Ct values for IAV, IBV, and RSV, with coinfected index cases having higher Ct values than singly infected index cases (Supplementary Fig. 1). The individual-level models for IAV and RSV were stratified by the age of household contacts to determine whether age may affect the associations between the main predictors and infection risk; the IBV analysis was underpowered, so we were unable to stratify this model by age. When the IAV model was stratified by age (0–5, 6–17, and 18+ years), exposure to a coinfected index case remained negatively associated with IAV acquisition for all ages (Supplementary Table 3). When examining the relationship between contacts infected with another virus and transmission of IAV, stratifying by age resulted in an OR of 5.02 (95% CI 1.75–14.35, $P = 0.003$) for those aged 0–5, 3.60 (95% CI 1.35–9.58, $P = 0.010$) for those aged 6–17, and 2.43 (95% CI 0.80–7.42, $P = 0.118$) for those aged 18+. Exposure to a coinfected index case among contacts infected with a different virus was associated with an increased acquisition risk for those aged 6–17 (OR 3.54; 95% CI 1.17–10.66, $P = 0.025$) but not for the other age strata. In the RSV analysis stratifying by ages 0–17 and 18+, exposure to a coinfected index case remained negatively associated with virus acquisition for those aged 0–17 (OR 0.17; 95% CI 0.06–0.60, $P = 0.006$), but was not significant for those aged 18+ (Supplementary Table 4). In the second age-stratified RSV analysis, exposure to a coinfected index case was negatively associated with acquisition of RSV for those aged 0–5 (OR 0.14; 95% CI 0.04–0.52, $P = 0.003$) and those aged 6+ (OR 0.39; 95% CI 0.16–0.94, $P = 0.04$) (Supplementary Table 5). Infection with another virus among contacts remained positively associated with acquisition of RSV for all age strata. There was a significant association between exposure to a coinfected index case among contacts infected with

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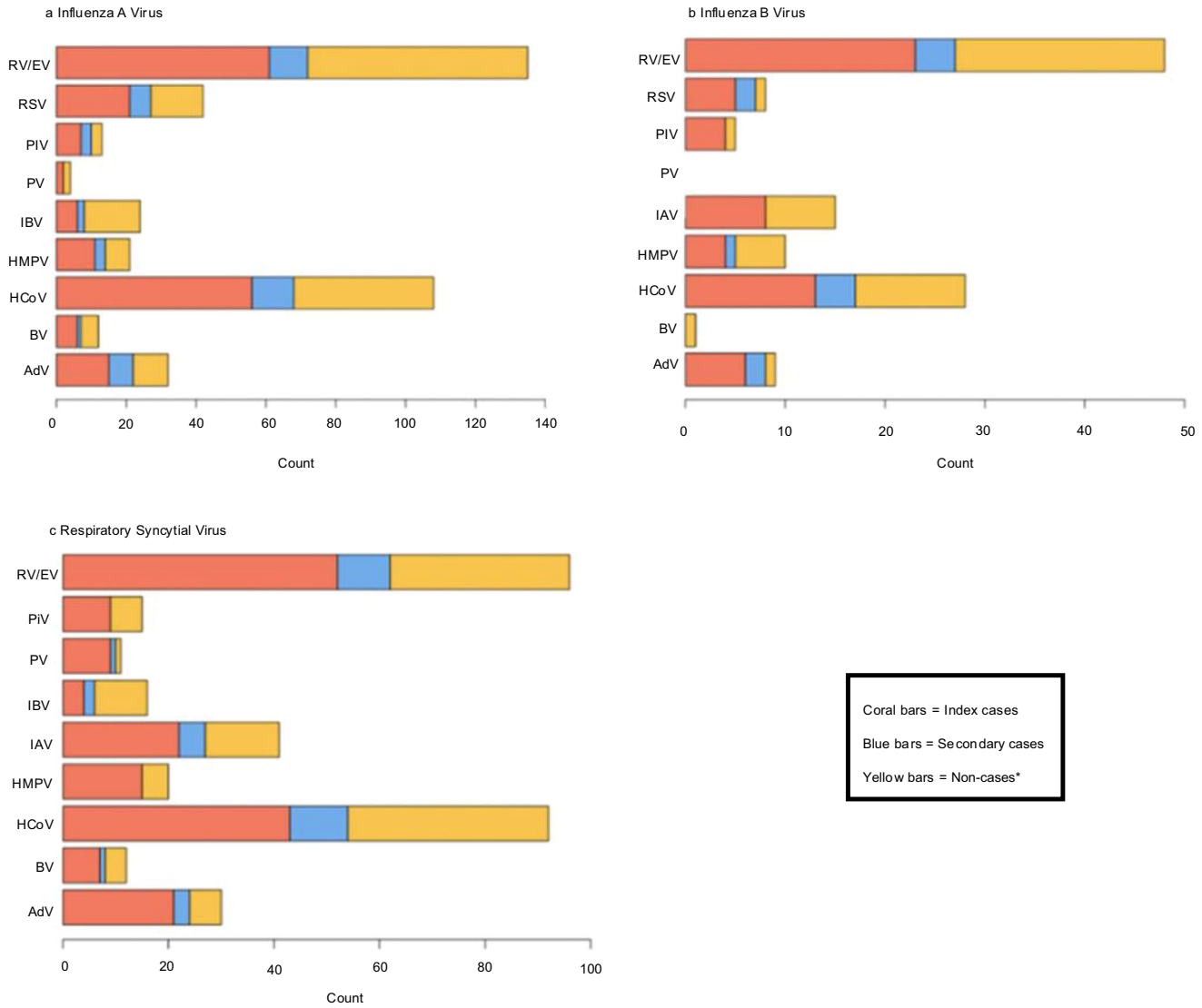

Fig. 2 | Viruses detected during household illness events, by primary virus of interest. a Other viruses detected during household illness events that involved influenza A virus. **b** Other viruses detected during household illness events that involved influenza B virus. **c** Other viruses detected during household illness events that involved respiratory syncytial virus. Source data can be found in Supplementary Tables 15–17, AdV adenovirus, BV bocavirus, HCoV human coronaviruses, HMPV human metapneumovirus, PV parechovirus, PIV parainfluenza virus, RV/EV rhinovirus/enterovirus. *Non-cases are those who were involved in a household illness cluster event for a virus of interest and did not test positive for the virus of interest.

another virus and acquisition of RSV in age stratum 6+ only (OR 3.36; 95% CI 1.01–11.12, $P = 0.048$).

We restricted the household- and individual-level analyses to RV/EV as the only viruses coinfecting/cocirculating with the viruses of interest to investigate whether the observed associations were the same when examining only these virus combinations; we repeated this for HCoV. In the RV/EV-restricted household-level analysis, exposure to a coinfected index case was negatively associated with transmission of IAV (IRR 0.20; 95% CI 0.09–0.43, $P < 0.001$); this was not significant for IBV or RSV (Supplementary Table 6). In the RV/EV-restricted individual-level analysis, exposure to a coinfected index case was negatively associated with acquisition of IAV (OR 0.20; 95% CI 0.09–0.46, <0.001) and RSV (OR 0.28; 95% CI 0.10–0.79, $P = 0.02$) (Supplementary Table 7). There was a significant association between infection with RV/EV and the acquisition of RSV among those exposed to singly infected index cases (OR 4.12; 95% CI 1.27–13.33, $P = 0.02$), but not IAV or IBV. There was not a significant association between exposure to a coinfected index case among contacts infected with RV/EV and acquisition of any virus. In the HCoV-restricted household-level analysis, exposure to a coinfected index case was not significantly associated with transmission of any virus (Supplementary Table 8). The HCoV-restricted individual-level analysis could only be performed for IAV and IBV. Exposure to index cases coinfected with HCoV remained negatively associated with acquisition of IAV (OR 0.30; 95% CI 0.13–0.69, $P = 0.004$) in the individual-level analysis (Supplementary Table 9). Infection with HCoV among contacts exposed to singly infected index cases had no significant association with acquisition of IAV or IBV. Exposure to an index case coinfected with IAV and HCoV among contacts infected with HCoV was associated with increased acquisition of IAV (OR 5.16; 95% CI 1.16–22.96, $P = 0.03$); this was underpowered for IBV and could not be assessed. In summary, the results of the RV/EV-restricted analysis were largely aligned with the main analysis. The results of the HCoV-restricted analysis were not significant except for exposure to coinfected index cases, which aligned with the main analysis, and infection with HCoV among contacts exposed to coinfected index cases which, unlike the lack of association in the main analysis, was positively associated with IAV acquisition.

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Table 5 | Results from household-level multivariable regression analyses using Poisson mixed-effects models examining the association between having a coinfected (versus singly infected) index case within the household and the incidence of virus transmission

Characteristic	IRR (95% CI)	*z* value	*P* value
Influenza A virus model[a]			
Coinfected index case	0.44 (0.29–0.66)	−3.895	9.81e-05
No. household members	0.91 (0.76–1.10)	−0.942	0.346
Index case <18	2.13 (1.46–3.10)	3.934	8.37e-05
Influenza B virus model[b]			
Coinfected index case	0.85 (0.39–1.84)	−0.423	0.672
No. household members	1.29 (0.94–1.78)	1.573	0.116
Index case <18	1.07 (0.47–2.42)	0.166	0.868
Respiratory syncytial virus model[c]			
Coinfected index case	0.51 (0.30–0.86)	−2.548	0.011
No. household members	1.03 (0.81–1.32)	0.249	0.803
Index case <18	1.24 (0.64–2.42)	0.636	0.525

In the influenza A virus analysis, there were 151 households with coinfected index cases and 395 with singly infected index cases. In the influenza B virus analysis, there were 54 households with coinfected index cases and 177 with singly infected index cases. In the respiratory syncytial virus analysis, there were 147 households with coinfected index cases and 223 with singly infected index cases. *P* values were computed using two-sided asymptotic Wald tests.

[a]Intraclass Correlation Coefficient (ICC) = 0.187, R^2 (conditional) = 0.223, R^2 (marginal) = 0.044, N = 546 household illness events.

[b]ICC = 0.248, R^2 (conditional) = 0.258, R^2 (marginal) = 0.013, N = 231 household illness events.

[c]ICC = 0.267, R^2 (conditional) = 0.280, R^2 (marginal) = 0.018, N = 370 household illness events.

To examine whether IAV subtypes may behave differently from each other, we stratified our analyses by IAV subtype. The directions of associations did not change for IAV H3N2 (Supplementary Tables 10 and 11). For IAV H1N1, the only significant association was between infection with a different virus and H1N1 acquisition in the individual-level analysis (OR 3.81; 95% CI 1.19–12.26, P = 0.03). Finally, to remove the possibility of inaccurately characterizing missed index cases as at-risk, we performed a household-level analysis excluding person-time at risk; exposure to a coinfected index case remained negatively associated with transmission of IAV and RSV (Supplementary Table 12).

Discussion

We used data from a prospective cohort study of households with children in Southeast Michigan to examine the possible effects of viral coinfection and cocirculation on household transmission of respiratory viruses. Separate analyses were conducted for three different viruses of interest: IAV, IBV, and RSV. Coinfection among index cases was associated with a reduced transmission of IAV and RSV in individual-level and household-level models. Despite significant differences in Ct value between coinfected and singly infected index cases, adjusting for Ct value of viruses of interest among index cases in the individual-level models did not change this relationship. Infection with a different virus among household contacts exposed to singly infected index cases was associated with increased acquisition of IAV and RSV. Exposure to a coinfected index case among contacts infected with another virus was associated with an increased risk of acquisition of IBV.

The possibility of viral interaction affecting respiratory virus transmission patterns has been hypothesized but primarily has been observed in ecologic studies that are unable to directly evaluate the mechanisms behind this phenomenon. Casalegno et al.[13] evaluated the hypothesis that rhinoviruses delayed the onset of the A(H1N1) 2009 influenza virus pandemic in France. The authors found that between

Table 6 | Results from individual-level multivariable mixed-effects logistic regression analyses examining the association between infection with a different virus and exposure to a coinfected index case with the odds of virus transmission

Characteristic	Influenza A virus model[e]			Influenza B virus model[d]			Respiratory Syncytial Virus model[e]		
	OR (95% CI)	*z* value	*P* value	OR (95% CI)	*z* value	*P* value	OR (95% CI)	*z* value	*P* value
Category 2: not infected with another virus, exposed to coinfected index[a]	0.39 (0.23–0.64)	−3.722	0.000198	0.56 (0.20–1.56)	−1.099	0.271592	0.28 (0.13–0.60)	−3.313	0.000922
Category 3: infected with another virus, exposed to singly infected index[a]	3.49 (2.02–6.03)	4.488	7.18e-06	2.16 (0.59–7.96)	1.162	0.245112	6.05 (2.55–14.35)	4.086	4.38e-05
Category 4: infected with another virus, exposed to coinfected index[a]	1.33 (0.64–2.75)	0.757	0.449338	5.39 (1.36–21.37)	2.398	0.016467	2.29 (0.93–5.68)	1.795	0.072647
Sex (male)	1.40 (1.01–1.93)	2.024	0.042963	0.78 (0.41–1.49)	−0.756	0.449592	0.84 (0.51–1.39)	−0.680	0.496274
Index case <18	2.58 (1.70–3.93)	4.420	9.89e-06	1.37 (0.51–3.65)	0.624	0.532469	1.76 (0.77–4.01)	1.344	0.178939
Age 6–11[b]	0.59 (0.36–0.95)	−2.164	0.030477	0.43 (0.18–1.04)	−1.881	0.059942	0.33 (0.16–0.65)	−3.184	0.001455
Age 12–17[b]	0.54 (0.30–0.97)	−2.048	0.040555	0.14 (0.04–0.51)	−2.974	0.002943	0.15 (0.05–0.43)	−3.518	0.000434
Age 18–49[b]	0.56 (0.36–0.86)	−2.605	0.009175	0.20 (0.08–0.46)	−3.785	0.000154	0.19 (0.10–0.36)	−5.255	1.48e-07
Age 50+[b]	0.62 (0.26–1.51)	−1.044	0.296570	0.10 (0.01–0.97)	−1.984	0.047300	0.28 (0.06–1.26)	−1.657	0.097599
Seasonal influenza vaccination >14 days prior to exposure	1.14 (0.79–1.63)	0.698	0.484948	1.34 (0.62–2.87)	0.743	0.457540	2.06 (1.11–3.81)	2.303	0.021291

In the influenza A virus analysis, there were 1177 individuals in exposure category 1, 431 in category 2, 107 in category 3, and 73 in category 4. In the influenza B virus analysis, there were 546 individuals in exposure category 1, 169 in category 2, 32 in category 3, and 25 in category 4. In the respiratory syncytial virus analysis, there were 719 individuals in exposure category 1, 408 in category 2, 58 in category 3, and 71 in category 4. *P* values were computed using two-sided asymptotic Wald tests.

[a]Reference group: Category 1—contact not infected with another virus, exposed to singly infected index case.

[b]Reference group: Age 0–5.

[c]ICC = 0.21, R^2 (conditional) = 0.304, R^2 (marginal) = 0.114, N = 1788 individuals.

[d]ICC = 0.41, R^2 (conditional) = 0.473, R^2 (marginal) = 0.113, N = 772 individuals.

[e]ICC = 0.38, R^2 (conditional) = 0.521, R^2 (marginal) = 0.191, N = 1256 individuals.

weeks 36 and 48 of 2009, both rhinoviruses and H1N1 were detected but in different timeframes. During a 3-week cocirculation period of these two viruses, rhinovirus detection appeared to reduce the likelihood of H1N1 detection, supporting the hypothesis that rhinovirus infection can inhibit H1N1 infection. Another study by van Asten et al.[14] investigated time trends and correlation between eight common viruses in the Netherlands over a 10-year period. The authors found that when IAV epidemics occurred earlier than usual, the epidemics of three other viruses were affected; RSV waves tended to be delayed, coronavirus outbreaks were intensified, and IBV tended to not appear at all.

Virus–virus interaction may manifest in several ways at the cellular, host, and population levels. Examples of cellular-level interaction may involve competition for host resources or certain viruses enhancing or inhibiting replication of other viruses[8]. At the host level, viruses may work synergistically or antagonistically to result in differences in disease severity than would occur if infected with only one of the viruses[15]. At the population level, viral interaction may result in more or less frequent coinfection of certain virus combinations than would be expected by chance alone or may impact the circulation of multiple viruses within a population[7,16]. The type of virus–virus interaction observed may depend on the specific combination of viruses involved[7]. Studies of viral interaction have historically been conducted at the host level through animal models[17,18], using clinical and cross-sectional data to assess illness severity[19,20], utilizing surveillance data to develop mathematical interaction models[21,22], and ecologically to quantify interference at the population level by examining the timing of virus waves[23,24]. We are aware of only one study that has examined the relationship between viral coinfection and respiratory virus transmission in humans. This study by Scott et al.[9] considered various predictors of household virus transmission in rural Nepal, and the authors found that viral coinfection among index cases was a risk factor for household transmission. Possible reasons for the differing findings between this study and the current study include differences in study populations, viruses tested, and ARI case definitions. Another study by Waterlow et al.[10] examined the interaction between influenza viruses and RSV but focused on how viral interaction impacts susceptibility to one virus when already infected with the other virus rather than transmission between individuals.

Our findings suggest that respiratory virus transmission may be impacted by other viruses coinfecting individuals and cocirculating within households. RV/EV and HCoV were the most commonly identified coinfecting and cocirculating viruses. RV has been shown to interfere with RSV[25] and influenza[26] infections. Pinky and Dobrovolny[27] used a mathematical model to investigate the kinetics of viral coinfections within the respiratory tract. They found that while RV was seemingly unaffected by the presence of other viruses, the replication of other viruses might be suppressed in the presence of RV. In the current study, in the RV/EV-restricted analyses, exposure to coinfected index cases remained negatively associated with IAV transmission in household- and individual-level models and with RSV acquisition in the individual-level model. Infection with RV/EV among contacts exposed to singly infected index cases was associated with an increased risk of RSV acquisition. In the HCoV-restricted individual-level analysis, exposure to an index case coinfected with IAV and HCoV was associated with decreased risk of IAV acquisition, but this association reversed when contacts were infected with HCoV and were exposed to a coinfected index case. This suggests that any protective association between exposure to a coinfected index case may be outweighed by the increase in susceptibility to IAV acquisition associated with HCoV infection. The same may be true for IBV and other coinfecting/cocirculating viruses, as contacts who were infected with another virus and exposed to a coinfected index case had an increased risk of IBV acquisition. One hypothesis for the observed protective association of exposure to coinfected index cases against transmission of IAV and RSV is that this may be driven by antagonistic relationships between RV/EV and RSV/IAV that specifically inhibit the transmission of these viruses of interest. The observed increased risk of acquisition of IAV and RSV associated with infection with another virus among household contacts correlates with the findings of the previously mentioned study by Waterlow et al.[10], which identified an increased risk of influenza infection during or shortly following RSV infection. Hence, it is possible that infection with certain viruses truly increases the risk of infection with IAV or RSV for some period of time post-infection.

The covariates in this analysis highlight several important associations. The age of household members may be associated with household transmission dynamics for many reasons. For example, Munywoki et al.[28] studied RSV illnesses within households in Kenya and found that school-aged children frequently were index cases within households, often leading to transmission to infant siblings. Also, having received a seasonal influenza vaccination at least 14 days prior to household exposure was not associated with reduced transmission of IAV or IBV and was associated with an increased transmission of RSV. Cowling et al.[29] identified an increased risk of non-influenza viruses after receipt of an inactivated influenza vaccine, and they proposed that this finding was related to a lack of non-specific immunity against other respiratory viruses in the absence of influenza infection. It is possible that this phenomenon is responsible for the apparent risk of RSV infection associated with receipt of influenza vaccination observed in the present study. The models used in this analysis are not intended to estimate vaccine effectiveness against influenza. Notably, the HIVE population may not be representative of many other populations, as it has relatively high levels of influenza vaccination. While not the focus of the present study, a more comprehensive analysis focused on influenza vaccination and the risk of non-influenza viruses could disentangle this relationship.

This study attempts to characterize the relatively unknown role that viral interaction plays in the transmission of respiratory viruses. The study has multiple strengths. The use of a prospective cohort study allowed for households to be followed for the entirety of their illness cluster windows. The breadth of data available through the HIVE study over the 10-year period from 2010 to 2020 allowed us to use multivariable analyses to examine multiple potential modes of virus–virus interaction for three different viruses of interest in households and individuals. We also conducted several sensitivity analyses which strengthened the findings of our main analyses. Because HIVE is a community-based study that utilizes active surveillance to identify ARIs, less severe illnesses that did not require medical attention—and therefore are often excluded from studies that utilize clinical data—were captured. The inclusion of mild illnesses is crucial for the comprehensive understanding of household virus transmission, especially when virus–virus interaction may be involved. Also, studying virus transmission within the household setting is ideal, as household exposures to respiratory viruses represent the highest-risk exposures, often involving interactions with close proximity for long durations of time.

It is important to note that the HIVE study required participants to meet a standard ARI definition to be eligible for testing; thus, asymptomatic infections were not captured in the present study. This could have led to bias in our study in several ways. First, coinfected index and secondary cases could have been differentially ascertained in terms of coinfection status if coinfections were more or less likely to exhibit respiratory illness symptoms than singly infected cases. For example, if coinfected secondary cases were more likely to be detected than singly infected secondary cases, this would have inflated the association between infection with another virus and acquisition of a virus of interest. A second concern is that index and secondary cases may have been missed if they were asymptomatic. If a singly infected asymptomatic index case transmitted a virus of interest to a household contact who became coinfected and met the ARI case definition, this

coinfected case would have been identified as the index case. This misclassification of the index case could have multiple implications. Subsequent transmissions may have resulted from the true index case but were attributed to the coinfected case; if so, the protective association between exposure to coinfected index cases and transmission would have been attenuated in our analysis. Another implication of this misclassification is that the asymptomatic true index case would be included in the pool of at-risk individuals even though they were no longer at risk for the outcome. In our household-level analyses, we accounted for person-time at risk for each exposed household member, and any missed index cases would have contributed at-risk person-time. This could have made the association between exposure to coinfected index cases appear stronger than it truly was or even made it appear protective against transmission when it truly was not. However, results from the household-level sensitivity analysis that excluded person-time at risk were in the same direction as our main analysis, indicating that this misclassification may not have greatly biased our results in this way.

Population rates of asymptomatic viral infections may be quite high, but estimates vary according to the populations involved and differing definitions of what it means to be asymptomatic[30]. Studies comparing symptomatology between coinfections and single virus infections have had mixed results[19]. Kim et al.[31] examined coinfections between influenza viruses and human OC43 coronavirus in normal human bronchial epithelial cells and found that while coinfection with OC43 did not affect replication of IAV or IBV, select cytokine/chemokine expression was increased in coinfected cells compared to singly infected cells. A household study of infants in Nepal[32] found coinfection to be associated with an increased risk of fever lasting 4 or more days but not with any other measures of illness severity. A study among childcare attendees in the United States[33] found that children with multiple viruses identified at the onset of illness had less frequent fever but more often had illness lasting over 7 days. Another community-based study in the United States[34] showed that coinfection was not associated with the presence or severity of symptoms compared to single virus infections and that influenza and human metapneumovirus were associated with more symptoms than other viruses. A community-based birth cohort study of children aged 0–2 years in Australia found that viral codetections may be associated with a higher risk of lower respiratory tract infection compared to certain single virus infections, but risk for the presence or absence of ARI symptoms appeared to be similar for single virus infections and multiple virus infections[35]. The results of these community-based studies suggest that coinfected cases would not necessarily have been more likely to meet the ARI case definition required for testing than singly infected cases. Young children are less often asymptomatic when experiencing respiratory viral illness compared to other age groups[36], so we would expect that estimates within the 0–5 age stratum would be less affected by any misclassification resulting from the omission of asymptomatic cases. In sensitivity analyses, the relationships between predictors and virus transmission among this age stratum were similar to those in the main analysis. Still, it is important to note that our findings may only apply to symptomatic infections.

This study has other limitations that should be acknowledged. The detection of a virus in the respiratory tract does not necessarily indicate a current infection, but rather may indicate a recently resolved infection or asymptomatic shedding. This may have affected our results due to impacts on viral load, such as reduced viral loads for persistent or recently resolved infections resulting in lower transmissibility that is unrelated to viral interaction. Similarly, the observed reduction in transmissibility from coinfected index cases may be overestimated due to the ascertainment of mild, less transmissible infections that would not have been detected without symptoms largely driven by the coinfecting pathogen. Although adjusting for Ct value of viruses of interest among index cases did not change the direction or magnitude of our results, it is possible that the relationship between coinfection, viral load dynamics, and transmission is more complex than what we could account for in this analysis. Similarly, the co-detection of viruses may not represent true coinfection, which could have resulted in misclassification of some index and secondary cases as coinfected when they did not truly experience concurrent infection with multiple viruses. However, viral interaction may be present when one virus infects a host subsequently after another[26]. Therefore, despite the inability to differentiate between concurrent and successive infections, viral interaction could have occurred, nonetheless. There was the possibility of misclassification of secondary cases in the absence of sequencing to confirm household transmission versus community acquisition. However, two studies that utilized molecular testing to examine influenza virus transmission within HIVE households identified that the majority of select IAV[37] and IBV[38] index-secondary case pairs represented true household transmission. Coupled with the high-risk nature of household exposures, this suggests that such misclassification may be minimal in our study.

We were likely unable to completely account for underlying differences in susceptibility that may be common for the acquisition of multiple respiratory viruses, which is often a limitation in studies of ARI. There are many factors that are associated with how at-risk a household member is, including comorbidities, age, daycare attendance, and birth order, to name a few. These interwoven factors operate in a complex manner within households, and we may not have completely accounted for these in our analysis. As such, we cannot rule out the possibility that our findings are confounded by differences in infection risk between coinfected and singly infected participants and within members of households with multiple viruses circulating versus a single virus. Our findings require further investigation in other settings in which the underlying susceptibility of participants may be better defined. Finally, while we were able to restrict our analyses for IAV subtypes, we were unable to do so for RSV, and it is possible that RSV A and B may behave differently.

Understanding the ways in which influenza viruses and RSV interact with other viruses could inform public health planning and prevention efforts, especially in preparation for seasons with exceptionally high levels of these viruses or the circulation of multiple viruses simultaneously, as transmission may be heightened or reduced depending on the viruses involved. As Opatowski et al.[39] concluded, evaluating influenza viruses in isolation may lead to an incomplete picture of the burden they pose, which in turn may hinder public health prevention efforts. The same could be argued for RSV.

This study provides insight into the ways in which virus–virus interaction may impact the transmission of influenza and RSV within households. This interaction may occur at the level of the individual introducing the virus into the household, blocking transmission to exposed household members. This interaction also may occur within the household contact, encouraging dual infection of certain viruses. Future research should focus on delving further into the interaction dynamics of different virus combinations, as well as utilizing serial testing to identify asymptomatic infections and establish infection temporality.

Methods

Study population

The HIVE study is an ongoing prospective cohort study of households with children in Southeast Michigan, USA that began in 2010 and allows for the study of multiple respiratory pathogens and their transmission dynamics within households. The present study utilized data from HIVE study years 2010–2020. Additional details about the study population have been previously described[40]. Written informed consent (paper or electronic) was obtained from adults (aged >18). Parents or legal guardians of minor children provided written informed consent on behalf of their children. Participants were compensated for their time and effort. The HIVE study is approved by the

institutional review board at the University of Michigan Medical School (HUM00034377 & HUM00118900).

Data and specimen collection

Active, weekly ARI surveillance using a standard case definition was conducted seasonally from October to May in 2010–2014, and beginning in October 2014, year-round surveillance was performed. From 2010 to 2014, all respiratory specimens associated with an illness were collected by study personnel at illness visits. Starting in 2014, adult household members were trained to also collect nasal specimens from themselves and their participating children at study enrollment visits and were instructed to collect specimens upon onset of a respiratory illness in addition to specimens collected at study visits[41]. Specimens collected at study visits were the default specimens tested; however, there were several instances in which self-collected specimens were used, such as when participants were unable to attend illness visits. Starting in the spring of 2020, all respiratory specimens were self-collected, which included three specimens corresponding to IAV clusters, three corresponding to RSV clusters, and none corresponding to IBV clusters. When a household reported an illness, study staff contacted the household to coordinate specimen collection for those that met the ARI case definition. The case definition required two or more of the following symptoms: fever/feverishness, cough, nasal congestion, sore throat, body aches, chills, and headache; starting in 2014–2015, a separate ARI definition was used for those <3 years of age, requiring two or more of the following symptoms: fever/feverishness, cough, nasal congestion/runny nose, trouble breathing, fussiness/irritability, fatigue, and decreased appetite. Study participants were not notified of their specimen testing results and were not issued infection prevention instructions by the study team. Longitudinal data on demographics, detailed health history, and influenza vaccination status were also collected via self-report at the annual enrollment/re-enrollment visits. In addition to self-reported health history and influenza vaccination, these data were also collected via electronic medical records and the Michigan Care Improvement Registry.

Laboratory testing

Respiratory specimens were tested for influenza viruses using the US Centers for Disease Control and Prevention (CDC) Influenza Virus Real-time reverse transcriptase polymerase chain reaction (RT-PCR) Influenza RUO Assays[42], then batch-tested for a panel of other respiratory viruses, including adenovirus, bocavirus, HCoV (229E, NL63, OC43, and HKU1), enterovirus, human metapneumovirus, parainfluenza virus, parechovirus, rhinovirus, and RSV. Prior to the 2016–2017 study year, specimens were tested using singleplex RT-PCR with primers and probes from the US Centers for Disease Control and Prevention. Specimens collected during the 2016–2017 study season and beyond were tested using the Fast Track Diagnostics (FTD) Respiratory Pathogen 21 multiplex PCR kit (FTD-2-64-RUO, SMN: 11373928, Siemens Healthineers, Malvern, PA). Positive specimens were determined based on the presence of an amplification curve and virus-specific Ct was recorded for all positive results. Laboratory testing was performed at the University of Michigan School of Public Health.

Study definitions

As study participants were required to meet a syndromic definition to be tested, the positive identification of a respiratory virus was considered an infection. Viral coinfection was defined as the simultaneous detection of more than one respiratory virus from a respiratory specimen. For example, a coinfection in the IAV analysis involved the detection of IAV and any other respiratory virus. RV/EV were grouped together. The household member who first exhibited symptoms prior to testing positive for a virus was considered the index case. If multiple household members developed symptoms on the same day, they were deemed co-index cases and were not included as at-risk household members. A household transmission event occurred whenever a secondary case matching the respiratory pathogen of the index case within the same household occurred 1–14 days following the index case's illness onset. The at-risk period for household members spanned the 14 days following a case's illness onset and was extended each time another household member became a secondary case. The household's illness cluster window ranged from the illness onset of the index case to 14 days following the final secondary case's illness onset. When examining household transmission of each virus of interest, all initial viral infections within a household were preceded by at least 14 days without an identified infection caused by the virus of interest. A household contact was determined to be infected with a virus other than the primary virus of interest if they tested positive for another virus during the household illness cluster window.

Statistical analysis

The proportion of secondary cases that made up the total case count for each virus and the proportion of cases that were coinfected were compared across viruses using Pearson's Chi-squared test for homogeneity. We explored viral interaction by evaluating two main predictors of transmission: coinfection in the index case and detection of a virus other than the primary virus of interest in the household contacts. Household- and individual-level analyses were conducted three times—once for each virus of interest, including IAV, IBV, and RSV. For the IAV analysis, any non-IAV virus was considered as a coinfecting or cocirculating virus, including IBV and RSV. Similarly, any non-IBV virus was examined for interaction in the IBV analysis, and any non-RSV virus was examined in the RSV analysis. Serial intervals, which is the time from symptom onset of the index case to the symptom onset of the secondary case, were calculated by virus. Data analysis was performed using R software version 4.3.1 (R Foundation for Statistical Computing). The mixed-effects regression analyses were performed using the lme4 package and the models were fit by maximum likelihood (Laplace Approximation).

To estimate the household risk of virus transmission within households with coinfected index cases while accounting for total person-time at risk, a household-level analysis was performed. Coinfection versus single infection among index cases was the primary predictor and the outcome was the number of virus transmissions in the household. Each household illness event was condensed into a single data point, and multivariable regression with Poisson mixed-effects models was used to associate coinfection among households' index cases with the incidence of transmission of the virus of interest (IAV/IBV/RSV), adjusting for household size and age (<18 and ≥18 years) of the index case. Random intercepts were included to account for household clustering. Two-sided P values were calculated using Wald tests at the 0.05 level.

To estimate an individual's risk of infection when multiple viruses circulated simultaneously within their household while accounting for individual-level factors, an individual-level analysis was performed. The main predictor was a four-category variable with different combinations of exposure to a coinfected index case and infection with a virus other than the primary virus of interest (Fig. 3). Category 1 represents contacts who were not infected with another virus and were exposed to a singly infected index case; category 2 includes those who were not infected with another virus and were exposed to a coinfected index case; category 3 includes those who were infected with another virus and exposed to a singly infected index case; category 4 represents those who were infected with another virus and were exposed to a coinfected index case. We examined the association between this predictor and the transmission of each virus of interest using mixed-effects logistic regression models with random intercepts to account for household clustering. The age (<18 and ≥18 years) of the index case was included as a household-level covariate. Individual-level covariates included sex, age group (0–5, 6–11, 12–17, 18–49, and 50+), and

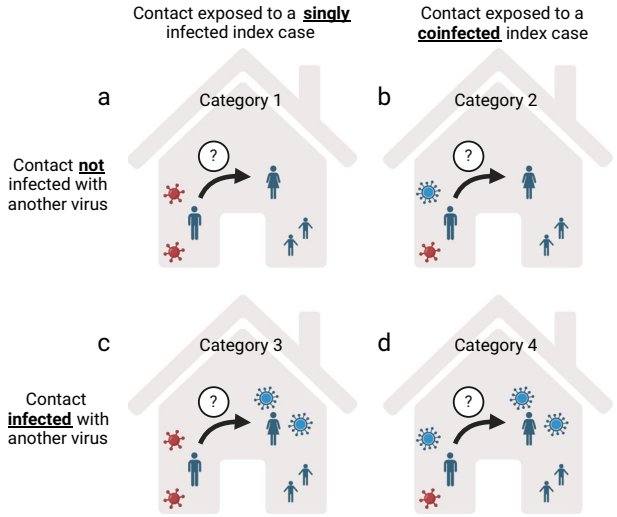

Fig. 3 | Four-category exposure variable used in multivariable mixed-effects logistic regression models. a Exposure category 1 includes household contacts who were not infected with another virus and were exposed to a singly infected index case. **b** Category 2 includes those who were not infected with another virus and were exposed to a coinfected index case. **c** Category 3 includes those who were infected with another virus and were exposed to a singly infected index case. **d** Category 4 includes those who were infected with another virus and were exposed to a coinfected index case. Created in BioRender. Ibiebele, J. (2025) https://BioRender.com/x27o890.

vaccination status (receipt of seasonal influenza vaccine ≥14 days prior to household exposure event within the same season) of household contacts. A summary of alternative statistical models tested is included in the supplementary material (Supplementary Table 13). Model equations can be found in the supplementary material (Supplementary Table 14).

Covariates were selected a priori using a causal inference framework. Presence of at least one underlying high-risk comorbidity was considered for inclusion, but there was a small proportion of study participants with any high-risk comorbidity, so this variable was excluded from analyses. Self-reported sex, age group, and influenza vaccination status were compared by case status of each virus to the overall HIVE cohort study population from 2010 to 2020.

We performed several sensitivity analyses. First, the individual-level analysis was conducted using a transmission definition that required a positive test 2–14 days following the illness onset of the index case, rather than 1–14 days, to account for potential misclassification of co-index cases as secondary cases. Any cases that were positive the day after an index case were characterized as co-index cases. This sensitivity analysis was performed for IAV and RSV models, but we were unable to do so for IBV due to sample size constraints. Next, as a proxy for viral load, another sensitivity analysis included the RT-PCR Ct value of the virus of interest for index cases as a continuous variable in the individual-level models. Additionally, Ct values for IAV, IBV, and RSV were compared for coinfected versus singly infected index cases using Mann–Whitney *U* tests and box and whisker plots. A third sensitivity analysis stratified the individual-level analyses by age groups to the smallest level of granularity that still allowed for model convergence. For IAV, age was stratified into 0–5 years, 6–17 years, and 18+ years. For RSV, age was stratified into groups 0–17 and 18+ and then again into groups 0–5 and 6+. The analysis could not be stratified by age for the IBV analysis. In order to eliminate the possibility of unintentionally including missed asymptomatic index cases in the pool of at-risk individuals, we conducted the household-level analysis excluding person-time at risk. From this sensitivity analysis, we evaluated the direction and significance of beta coefficients compared to the main analysis to determine whether the possible inclusion of missed asymptomatic index cases skewed the results to show a negative association between exposure to coinfected index cases and household transmission when there was in fact either a positive association or no association. Also, we performed the household- and individual-level analyses restricting to only households with RV/EV as the coinfecting/cocirculating viruses, then with only HCoV as the coinfecting/cocirculating viruses. The individual-level HCoV-restricted RSV model did not converge. Finally, we also performed the IAV analysis stratified by subtype.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data sets generated and analyzed during the current study are available upon request. Access to data is controlled due to IRB considerations, as HIVE is an ongoing study. As is required through the Centers for Excellence in Influenza Research and Response (CEIRR) Network, those requesting access must fill out a data and specimen collaboration form that will be reviewed by investigators. To request access, please contact hivestudy@umich.edu. Initial responses to requests can be expected in 2–3 business days.

Code availability

Scripts necessary to replicate the main analyses from the current study are available on github (https://github.com/MCRVRR-code/JCI-Dissertation)[43].

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Author contributions

J.C.I. conceptualized the project, planned and performed the statistical analysis, interpreted the results, and drafted and revised the article. E.T.G. validated the statistical analysis and revised the article. A.P.C. coordinated the HIVE study, performed data curation, and revised the article. M.R.S. performed data curation. E.J. performed HIVE specimen testing. R.T. oversaw and performed HIVE specimen testing and revised the article. M.C.E., A.S.L., S.C,. and A.S.M. provided intellectual guidance and revised the article. E.T.M. conceptualized and oversaw all aspects of the project and revised the article.

Competing interests

The authors declare no competing interests.

Additional information

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