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Interplay Between Viral Shedding, Age, and Symptoms in Individual Infectiousness of Influenza Cases in Households

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Background. Understanding factors affecting the infectiousness of influenza cases is crucial for disease prevention and control. Viral shedding is expected to correlate with infectiousness of cases, but it is strongly associated with age and the presence of symptoms.

Methods. To elucidate this complex interplay, we analyze with an individual-based household transmission model a detailed household transmission study of influenza with 442 households and 1710 individuals from 2008 to 2017 in Hong Kong, to characterize the household transmission dynamics and identify factors affecting transmissions.

Results. We estimate that age, fever symptoms, and viral load were all associated with higher infectiousness. However, by model comparison, the best model included age and fever as factors affecting individual infectiousness, and estimates that preschool and school-aged children were 317% (95% credible interval [CrI], 103%, 1042%) and 161% (95% CrI, 33%, 601%) more infectious than adults, respectively, and patients having fever had 146% (95% CrI, 37%, 420%) higher infectiousness. Adding heterogeneity on individual infectiousness of cases does not improve the model fit, suggesting these factors could explain the difference in individual infectiousness.

Conclusions. Our study clarifies the contribution of age, symptoms, and viral shedding to individual infectiousness of influenza cases in households.

Keywords. influenza; transmission; infectiousness; viral shedding; symptoms.

On average, influenza viruses cause annual epidemics and occasional pandemics, bringing a high public health burden every year globally [1]. Understanding the determinants of infectiousness of cases is important to guide epidemic prevention and control. Viral loads had been considered as one important correlate to infectiousness of cases [2–4], with assumptions that viral load is proportional to infectiousness, and using duration of viral shedding as a proxy of duration of infectiousness [3, 5–11]. However, the evidence of this correlation was still limited and needed further investigation. By contrast, several studies reported that children were in general more infectious than adults [4, 12–15]. Moreover, it was expected that the presences of symptoms may be associated with higher infectiousness, such as fever [14]. On the other hand, these 3 factors were highly correlated: a higher symptomatic proportion in children [16, 17], child cases were associated with higher viral loads [18], and symptomatic cases had a higher viral load [2, 3, 19]. Clarifying their complex interplay in determining the infectiousness of cases could improve our assessment of correlates of infectiousness.

The household is an important setting for influenza transmission [12, 20] and is estimated to account for 30% of influenza transmission [21–23]. When there are infected household members, the risk of infection among their household contacts often increases to 10%–20% [24]. Case-ascertained household transmission studies recruited an index case and followed their household members for about 1 to 2 weeks, which was the infectious period of index cases and hence transmissions could be recorded [25, 26]. In previous case-ascertained household studies, with detailed records of characteristics of cases and contacts, factors affecting susceptibility or infectiousness could be detected by Fisher exact test or logistic regression [12, 13, 15], but assumed that secondary cases were all infected from index cases. To relax this assumption, we adopted an individual-based household transmission model that was previously developed to account for community and tertiary infections within the households to describe household

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transmission dynamics [14, 25–30]. Using this approach, we analyzed data from a household transmission study in 2008–2012 in Hong Kong, and found that viral load is at most a weak proxy of infectiousness, but the sample size was insufficient [14]. Here, we conduct a more comprehensive analysis of the household transmission study from 2008–2017, to explore the interplay between viral load, age, and symptom by rigorous model comparison technique, to identify the determinants of individual infectiousness of cases.

METHODS

Study Design

We conducted large, community-based studies on household transmission of the influenza virus in Hong Kong [7, 31] from 2008 to 2017. In these studies, we recruited outpatients with acute respiratory illness within 2 days after illness onset who lived in households with at least 2 other persons, none of whom reported recent illness in the preceding 14 days before the time of the first visit. They were then tested using the QuickVue Influenza A+B test (Quidel). We further followed up participants with positive results on the rapid test, along with their household contacts, involving 3 home visits over approximately 7 days. During each home visit, nose and throat swab specimens were collected from all subjects and their household contacts, regardless of the presence of respiratory symptoms. Daily symptoms for index cases and their household contacts were recorded in symptom diaries for the duration of follow-up.

Participants recruited from January 2008 to June 2009 were part of a randomized controlled trial of enhanced hand hygiene with or without surgical face masks, randomly allocated on a household basis [31]. Participants subsequently recruited in the summer of 2009 and afterward were part of a comparative study of seasonal and pandemic influenza virus transmission in households, and a simple hand hygiene intervention was given to all households [7]. Only households in which index cases had polymerase chain reaction (PCR)-confirmed influenza A virus infection were included in our analyses.

Laboratory Methods

The laboratory methods including specimen collection and transport, and the quantitative reverse transcription PCR assay used to detect and determine the molecular viral loads against influenza A and B viruses in respiratory swab specimens were described previously [31–34]. Briefly, paired nasal and throat swabs were pooled immediately after collection in a viral transport medium and delivered to the laboratory for cryopreservation at −70°C within 24 hours of collection. Total nucleic acid was extracted by using the NucliSens easy MAG extraction system (bioMerieux) according to the manufacturer's instructions. Twelve microliters of extracted nucleic acid with a random primer were used to prepare complementary DNA by using an Superscript III kit (Invitrogen) [33]. Detection of influenza A virus was conducted in a PCR assay with the inclusion of reference standard prepared using pCRII-TOPO vector (Invitrogen) containing the corresponding target viral sequences as previously described [32]. At the end of the assay, PCR products were subjected to a melting-curve analysis to determine the specificity of the assay. The lower limit of detection of the PCR assay was approximately 900 virus gene copies per milliliter.

Definition of Infections and Symptoms

PCR-confirmed influenza virus infection was defined as a positive result on testing of ≥1 nasal and throat specimen collected during the follow-up period. Illness onset time for PCR-confirmed influenza virus infection was defined as the first day when the subject reported ≥2 of the following 7 signs or symptoms: runny nose, cough, sore throat, headache, phlegm, myalgia, and fever [29]. Households that included >1 person with symptom onset at recruitment (ie, multiple index case patients) were excluded from the analyses.

Viral Shedding Trajectories Model

Given that index cases were recruited on different days after symptom onset, to fairly compare their levels of viral shedding, we adopted log-linear mixed-effect regression models to impute complete viral shedding trajectories of infected members, using observed viral load in PCR tests to impute how individual viral load changed with day after symptom onset, and considering the effects of being the index case in the household, receiving antiviral treatment, and the difference between children and adults [4, 9, 14, 35, 36]. Then, we predicted the viral load of infected members at symptom onset and divided them into low, medium, and high viral load groups accordingly (Supplementary Material Section 1). As a sensitivity analysis, we also extended the above model with random intercept and random slope, and dividing cases into low, medium, and high viral load groups based on viral load at symptom onset or area under the viral load trajectories (Supplementary Material Section 2 and Supplementary Figure 1).

Household Transmission Model

We aimed to determine the factors affecting susceptibility and infectiousness of cases. To achieve this, we employed an individual-based household transmission model (Supplementary Material Section 3) to explore factors affecting influenza A transmission in Hong Kong [25, 29, 30, 37]. The model described the risk of infections among household contacts as depending on the time since symptom onset of other infected household members, including both index cases and other infected household contacts. The model also allowed for the risk of infection from the community, which was assumed to be directly proportional to influenza

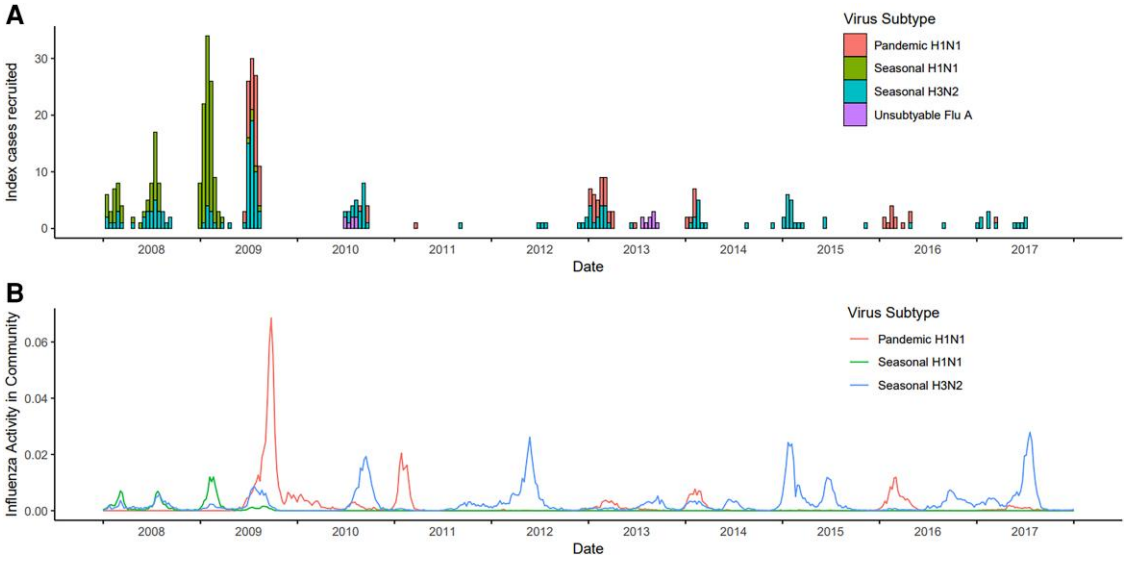

Figure 1. *A,* The number of index cases recruited at different times. *B,* The change of influenza activity of 3 virus subtypes in the community from 2008 to 2017.

incidence rates in the general community, proxied by local surveillance data [38], and estimating the constant of proportionality. The serial interval distribution was set based on a previous study [29], with a mean equal 2.7 days (Supplementary Table 1).

Model Specification

Age and influenza vaccination were factors that might influence susceptibility in household contacts and were put into all models. Oseltamivir treatment and subtype differences were factors that might influence infectiousness in cases and were put into all models [4, 7, 25, 26, 29, 39, 40]. We also considered age, viral loads, and fever as factors that might influence individual infectiousness and therefore we tested models with different combinations of these 3 factors to explore the interplay on affecting individual infectiousness [4, 26, 39]. Other symptoms including sore throat, cough, runny nose, phlegm, muscle pain, and headache were also tested by replacing fever with each of these symptoms individually in the model. Model parameters were estimated under the Bayesian framework by the Markov Chain Monte Carlo metropolis-hasting algorithm (Supplementary Material Section 3.6).

To further test if the considered factors could explain the variation in individual infectiousness, we adopted a previous approach [30] to determine if adding random effects to represent the differences in individual infectiousness of each case could provide a better fit (Supplementary Material Section 4).

Model Adequacy and Validation

Model validation was conducted by using the same procedures on model inference on datasets simulated by the mean of the posterior distribution of parameters estimated from the data, to demonstrate that our inference procedures could recover the model parameters (Supplementary Material Section 5). Model adequacy was assessed by using the estimated posterior distribution of parameters to simulate datasets and then comparing the expected and actual number of infections in households (Supplementary Material Section 6).

Model Comparison

The deviance information criterion (DIC) [41] was used as a measure of the goodness of fit to compare models. Smaller DIC indicated a better model fit. DIC differences >5 were considered to be a substantial improvement (Supplementary Material Section 7).

RESULTS

Study Participants

From 2008 to 2017, in total 559 households and 2184 members with positive PCR test results against the influenza A virus were enrolled in the study. Twenty households were excluded because the first PCR tests for their index cases were negative, and 80 households were excluded because they included >1 member with a positive result in the first PCR test. In addition, 8 more households whose data were incomplete and 9 households that had only 2 members (1 index case and 1 contact) were excluded as well. In total 442 index cases, with 1268 household contacts were included in the analysis (Figure 1). Among 442 index cases, 147, 182, 97, and 16 index cases with PCR-confirmed seasonal A(H1N1), seasonal A(H3N2), pandemic A(H1N1), and unsubtypable influenza A virus was included in our analysis, respectively.

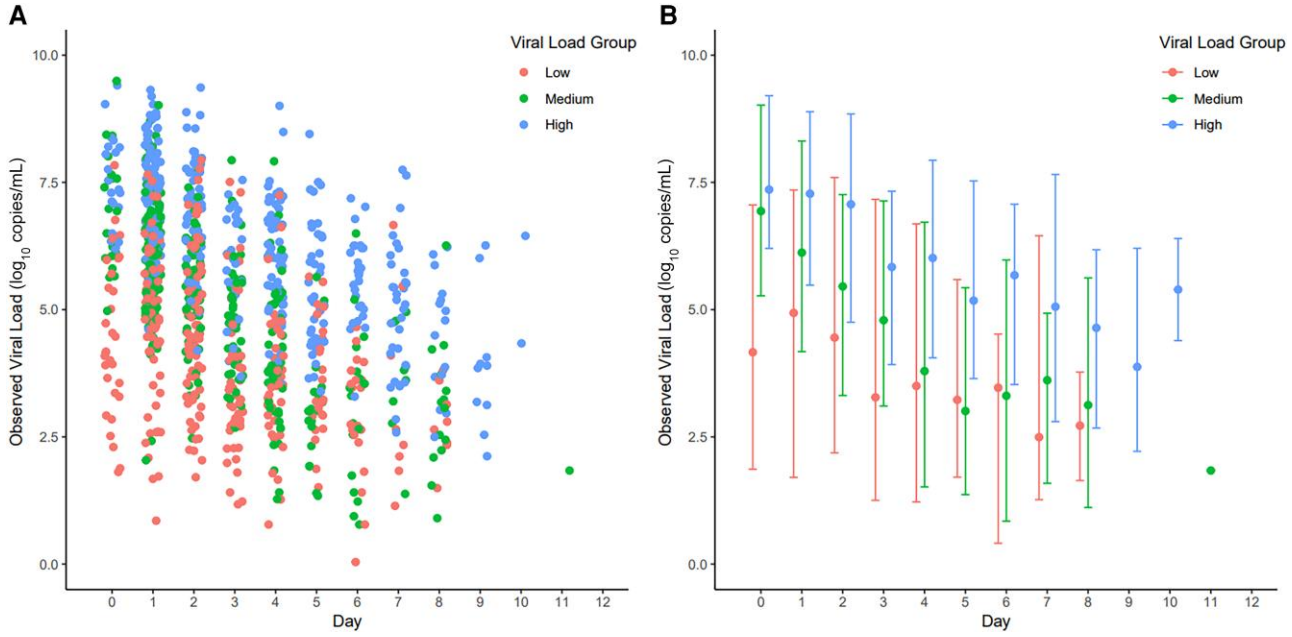

Figure 2. *A,* Observed viral load in polymerase chain reaction (PCR) tests against the number of days after symptom onset. Members were classified to 3 viral load groups according to their imputed viral load at symptom onset. *B,* Median and 95% quantiles of observed viral loads on each day of the 3 viral load groups.

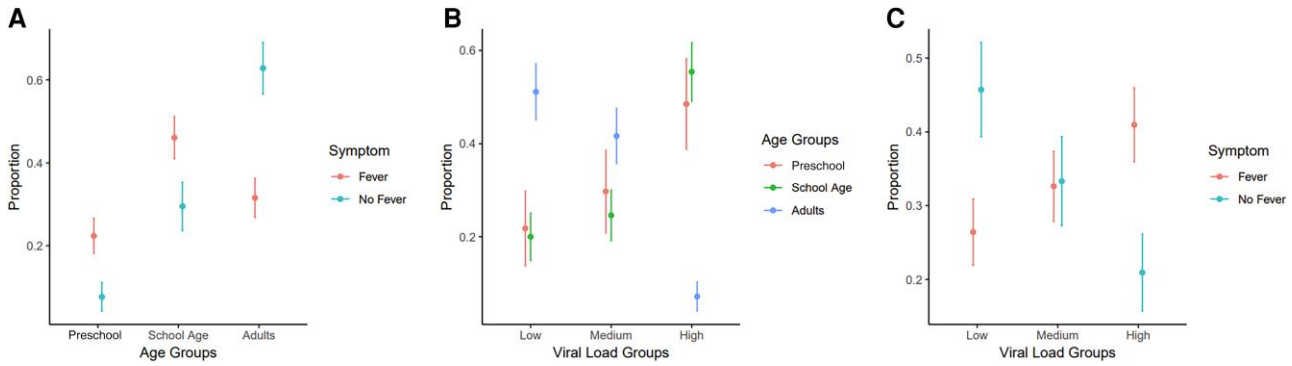

Figure 3. Correlation between factors age, viral load, and fever. The proportions and 95% confidence intervals of (*A*) adult and child infected participants with fever (red) and without fever (blue); (*B*) the viral load groups in infected preschool children (red), school-aged children (green), and adults (blue); and (*C*) the viral groups in infected participants with fever symptom (red) and without fever (blue).

We found that the observed viral load of index cases with seasonal A(H1N1) recruited at 2 days after symptom onset were higher than index cases with other subtypes ($P = <.01$, Kruskal-Wallis test) while other observed characteristics among index cases with different subtypes and their contacts were similar (Supplementary Table 2). We employed the linear mixed-effect regression model to predict the viral load at symptom onset for infected members, using their observed viral load in PCR tests [14], and then divided them into low, medium, and high viral load groups (Figure 2 and Supplementary Tables 3 and 4). Although the imputed viral load at symptom onset of index cases differed by virus subtypes ($P < .01$; Supplementary Table 2), the classification of viral load groups for index cases was not associated with their infected virus subtype ($P > .01$; Supplementary Table 4). In addition, the proportions of index cases and infected household contacts in 3 viral load groups were different among age groups; younger index cases were associated with higher viral shedding. Index cases classified into the medium viral load group were associated with lower secondary infection risk ($P < .01$, Fisher test and χ^2 test; Supplementary Table 4).

In addition, we found age, imputed viral load at symptom onset, and fever were correlated with each other (Figure 3 and Supplementary Tables 5 and 6). Both preschool (age ≤ 5 years)

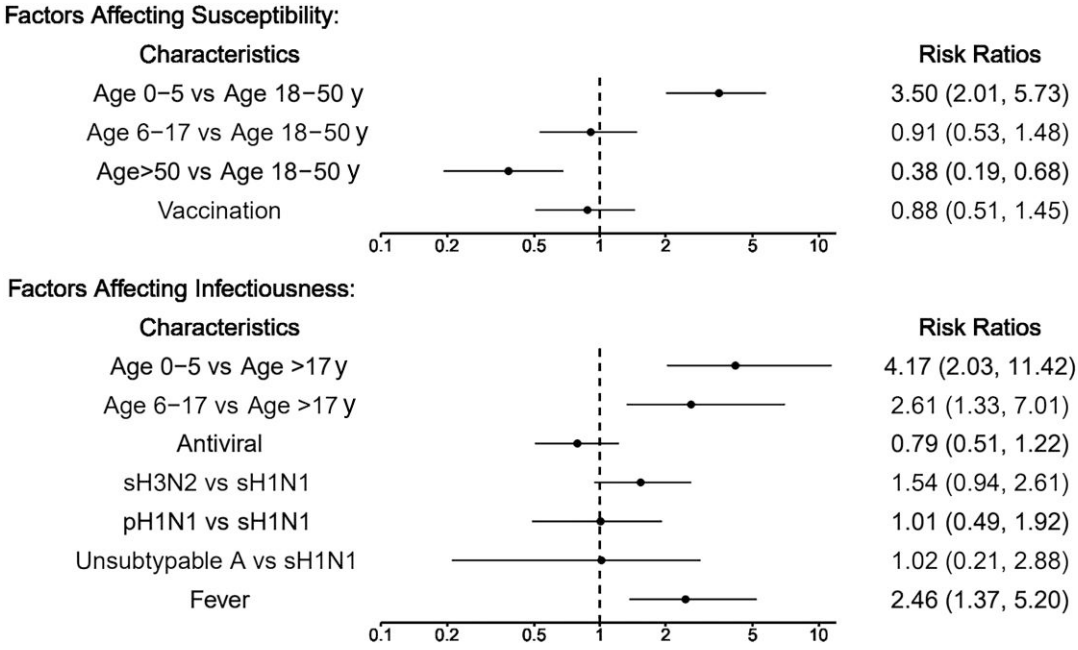

Figure 4. Estimated risk ratios and corresponding 95% credible intervals of characteristics affecting household transmission based on the main model.

and school-aged children (age 6–17 years) were more likely to have higher imputed viral load, and a high proportion in the high viral load group than adults. Children and higher viral load cases were more likely to have fever.

Household Transmission Dynamics

In the main model (selected based on model comparison in next section) [14, 25, 29, 37] (Figure 4), we estimated baseline person-to-person transmission probability among different subtypes were similar, ranging from 3.92%–5.97%.

We found that preschool children (age ≤ 5 years) were 250% (95% credible interval [CrI], 101%, 473%) more susceptible and older adults (age > 50 years) were 62% (95% CrI, 32%, 81%) less susceptible than younger adults (age 18–50 years). Preschool children were 4 times more infectious (relative hazard, 4.17; 95% CrI, 2.03, 11.42) than adults (age 18 years or older), while school-aged children also were associated with higher infectiousness (relative hazard, 2.61; 95% CrI, 1.33, 7.01). Moreover, infected household members who had fever symptoms were 146% more infectious (95% CrI, 37%, 420%). Vaccination, the use of antiviral and virus subtypes were not associated with household transmission.

The Interplay Between Age, Viral Load, Fever, and Infectiousness

In univariate analyses, age, fever and viral load were all associated with infectiousness in models that included only 1 of these 3 factors as covariates for infectiousness. We estimated that preschool and school-aged children had 443% (95% CrI, 159%, 1254%) and 207% (95% CrI, 52%, 638%) higher infectiousness than adults, febrile patients were 225% (95% CrI, 81%, 672%) more infectious than those who did not have fever symptoms, and cases in the higher viral load group were 99% (95% CrI, 11%, 285%) more infectious than lower viral load cases.

We tested models with different combinations of factors to quantify infectiousness (Figure 5, Supplementary Table 7, and Supplementary Figure 2). According to DIC comparison [41], we found that the main model (age + fever) was the best model. Except for the model with age, fever and viral load was comparable (ΔDIC = 0.16); models with other combinations of these factors were substantially worse. In addition, in models with viral load and any of age and fever, viral load was not associated with infectiousness, but we observed a weak and statistically insignificant increased effect (31%–67% higher infectiousness).

Regarding age, preschool and school-aged children were associated with higher infectiousness in all models. Among these models, preschool and school-aged children were associated with 278%–443% and 134%–207% higher infectiousness respectively. Regarding fever, in all models, cases with fever were also associated with higher infectiousness. Infected participants having fever symptoms were associated with 134%–225% higher infectiousness.

Based on the main model, we found adding a random effect to each case to represent a variation of individual infectiousness [30] (Supplementary Material 3.2) could not further improve the model fit (Supplementary Table 7; ΔDIC = 1.18). In the sensitivity analysis using a random intercept and slope model to classify cases to different group, the conclusion remained similar (Supplementary Figures 3 and 4).

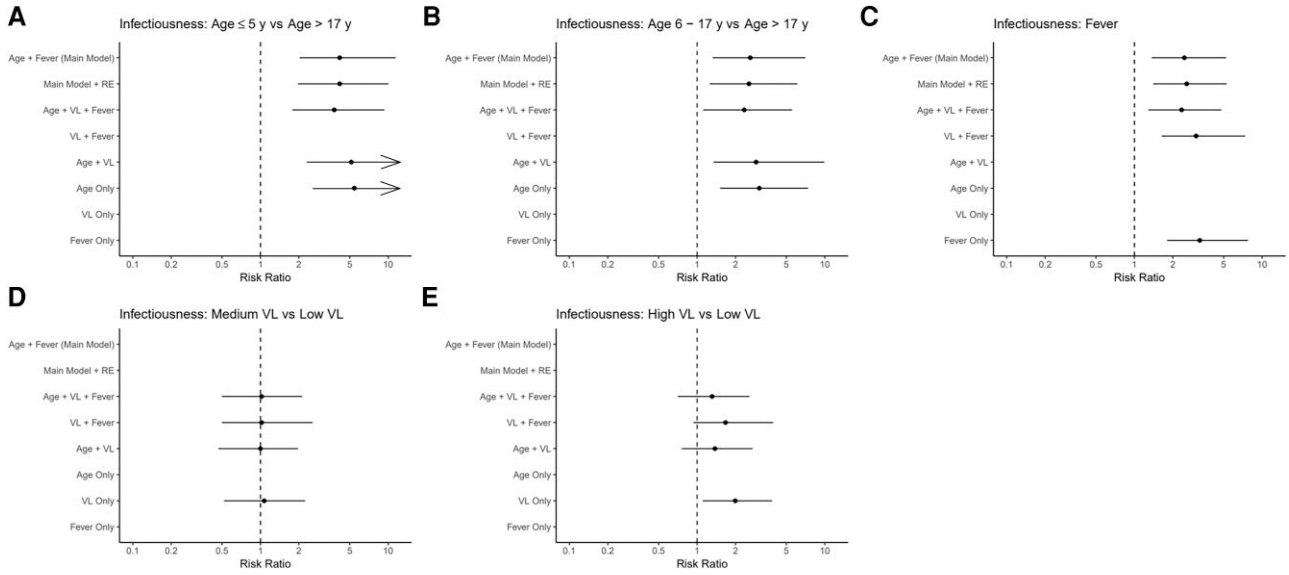

Figure 5. Risk ratios and 95% credible intervals of correlated factors affecting infectiousness in different models: (*A* and *B*) age; (*C*) fever; and (*D* and *E*) viral load. Abbreviations: RE, random effect; VL, viral load.

Model Variations

We tested different parametric forms of viral load to model infectiousness, including linear, log, quadratic, cubic, and exponential forms, instead of the nonparametric approach with 3 groups (high, medium, and low) in the main model (Supplementary Tables 8 and 9, and Supplementary Figure 5). Adding parametric forms of viral load into the main model did not improve the model fit (ΔDIC, −1.19 to 0.16).

The models including the 6 other common influenza symptoms rather than fever were substantially worse in terms of goodness of fit (ΔDIC > 5) and the added symptoms were not associated with infectiousness (Supplementary Table 10). The model using influenza-like illness (ILI) to replace fever provide similar fit but did not improve the model (ΔDIC = 1.54), in which ILI diagnosis was associated with 110% (95% CrI, 24%, 287%) higher infectiousness. Moreover, in all models including different symptoms, vaccination, the use of antiviral, and virus subtypes did not have effects on influenza A household transmission.

Model Adequacy and Validation

We simulated 10 000 datasets with parameter values drawn from the posterior distribution (Supplementary Table 11). The predicted final size distribution was consistent with the observed one, suggesting the model was adequate.

In a simulation study with 50 datasets simulated based on the final model with the mean of the posterior distribution, we found that there was no systematic bias (Supplementary Table 12). Moreover, 82% to 98% (depending on the parameter) of the 95% CrI covered the simulation value, suggesting that our approach could accurately estimate the posterior distribution.

DISCUSSION

In this study, we estimated the household transmission dynamics of influenza A virus, and explored factors affecting transmission. Age, fever symptoms, and viral load all associated with infectiousness when the other 2 factors were absent; however, only age and fever were selected in the best-fit model. Furthermore, we found that the use of an antiviral and virus subtypes were not associated with infectiousness, and adding random effect to characterize the variation of individual infectiousness could not improve the model fit. This suggested that age and the presence of fever could capture most of the variation in individual infectiousness.

Viral loads were expected to correlate with infectiousness [2–4], but our study found that viral loads were associated with higher infectiousness only when age and fever were not in the models. It was possible that the association between viral shedding and infectiousness could not be detected due to the limited sample size. On the other hand, child cases were associated with the lack of protection via cross-reactive antibodies acquired from past exposure to influenza, and hence higher viral load [16]. It was also possible that the viral loads in the throat and nose may not reflect the number of infectious viruses in the exhaled breath, as a previous study reported a low correlation between them [42]. Another possible reason was that in a dense environment with frequent contacts in households, patients with low viral loads could still effectively transmit the viruses, and hence the exact amount of virus load may not be important. Our results indicated that high viral loads could be an indicator of high infectiousness if other information was not available. However, when we considered age and

fever, viral loads were no longer important in determining the infectiousness of cases, which suggested identifying cases with higher infectiousness may not require the exact viral load information.

We estimated that preschool and school-aged children were associated with about 4 to 5-fold and 2 to 3-fold higher infectiousness compared with adults, which is consistent with previous studies [4, 12, 13, 15, 26]. One possible explanation is that children tended to have more frequent and intense contact with other household members [4, 15, 43], so they had a higher chance of infecting others. However, studies in South Africa [12] showed that middle-aged adults were more infectious, suggesting differences in contact patterns among countries may modify age-relative infectiousness. Considering the increased infectiousness of children, measures preventing cases in children, such as increasing vaccination coverage in children or school-based measures such as temporal suspension of classes with outbreaks could suppress the spread of the disease [44, 45].

We estimated that patients having fever were about 2 to 3 times more infectious than those without fever, suggesting fever could be a proxy of higher infectiousness. It may also be due to different contact patterns [14]. Patients with fever generally developed a series of sickness behaviors, including anorexia, fatigue, loss of interest in usual daily activities, social withdrawal, and cognitive dysfunction [46], which caused them to stay at home for rest and need to be cared for by family members. Therefore, one plausible explanation was that patients with fever had an increased frequency of closer contact with other household members. Our study supported the implementation of interventions targeting fever patients for the purpose of control and prevention, for example, fever screening for travelers. Although previous studies revealed that fever screening at borders and airports had only limited sensitivity for the detection of general influenza cases [47, 48], it could detect cases with fever symptoms and thus higher infectiousness, and hence it was still effectively contributing to the prevention of the spread of influenza.

We estimated that preschool children under 6 years old were associated with higher susceptibility, and older adults (age > 50) were associated with lower susceptibility than younger adults. This was consistent with previous studies, and possible explanations included lower level of preexisting immunity among younger household members [15, 20, 26–28], and the observation that the older adults tended to have a lower number of contacts with household members [4, 20, 28, 43].

Our study had several limitations. First, in this household transmission study, all index cases were recruited from outpatients with acute respiratory illness. Therefore, asymptomatic cases and cases having milder symptoms would not be included as index cases, which might limit the generalizability of our study results on the interplay between age, fever, and viral load, as asymptomatic cases did not have fever symptoms and could have different age distribution and viral shedding levels compared to symptomatic infections [14, 26]. Second, there could be misclassification of viral load groups. We tested different viral load trajectory models, and the conclusion remained the same. More sophisticated viral trajectories models could be adopted if more data on viral load were available. Furthermore, we tested a number of parametric and nonparametric forms of viral loads, but we may have missed some other forms of relationship between viral loads and infectiousness. Finally, although our model included various individual-level characteristics, there could still be other important and uncontrolled confounders, for instance socioeconomic status, which might affect the access to health care services, and hence susceptibility or infectiousness [14, 30].

In conclusion, we elucidated the complex interplay of viral loads, age, and the presence of fever in determining individual infectiousness. We found that age, fever, and viral loads were individually associated with higher infectiousness, but the best model only included age and fever. Our study supports control measures aiming at reducing transmissions for children and cases with fever.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. B. J. C. reports honoraria from AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Pfizer, Roche, and Sanofi Pasteur. All other authors report no potential conflicts.

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