

Background and Objectives

Influenza A viruses, including seasonal H1N1, seasonal H3N2 and pandemic H1N1, cause a high public health burden every year. Understanding the correlates of influenza transmission is important for both epidemic prevention and control. Identification of factors affecting infectivity and susceptibility can improve control measures, [5] for example isolation policy and vaccination distribution, by efficiently targeting at highly infectious or susceptible populations. In this study, we used an individual-based hazard model to analyze household transmission of influenza A virus in Hong Kong, to identify characteristics associated to the variation of infectivity and susceptibility.

Method

Study Overview

Outpatients with acute respiratory illness and their household members were recruited from 2008 to 2017. Each participant received three PCR tests to confirm infection status. In this study, we included households that had only one PCR-confirmed influenza A index case.

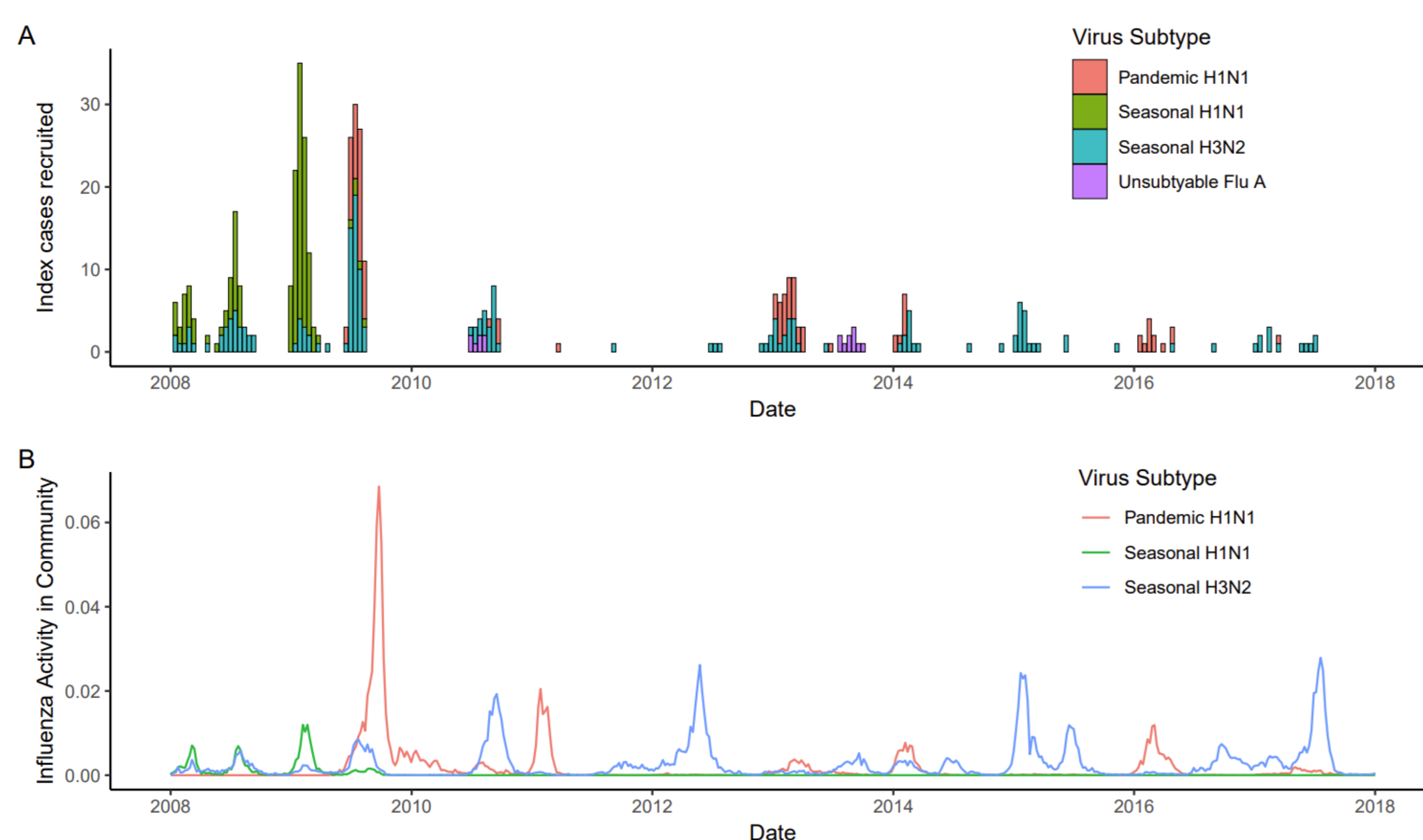


Figure: Panel A: the number of index cases recruited. Panel B: the change of influenza activity of three virus subtypes in the community from 2008 to 2018.

Model of Viral Shedding Trajectories

We adopted a log-linear mixed-effect regression model considering censored responses to impute viral shedding trajectories through the results of three PCR tests. [3] Infected participants were classified as low, medium and high viral load groups according to imputed viral load at symptom onset.

Household Transmission Model

We employed an individual-based household transmission model to explore factors affecting influenza A transmission in Hong Kong, describing the hazard for participants to be infected, either by the index case, an infected contact (tertiary infection) or other patients in the community. [2, 4]

The model included the hazard of infection from community, which was proportional to influenza activity, plus the sum of person-to-person transmission hazard within the household. The baseline hazard from household was inversely proportional to the number of household contacts due to the dilution effect, [4] and was multiplied by the infectiousness profile which was a function of the serial interval. Factors affecting infectivity and susceptibility were added and we evaluated their effects by estimating the values of corresponding coefficients. A random effect could be added to bring additional transmission heterogeneity.

Model Inference

Model parameters were jointly estimated by Bayesian Markov Chain Monte Carlo (MCMC) metropolis-hasting algorithm. The goodness-of-fit was measured by DIC value. [1] Model adequacy was assessed by comparing observed number of infected contacts in households and expected number simulated by the model. We also inferred the model on simulated datasets to validate the model.

Results

In total 451 index cases, with 1277 household contacts were included in the analysis. Selected according to the DIC criteria, our main model included age, vaccination as susceptibility covariates, age, antiviral treatment, virus subtypes and fever symptom as factors affecting infectivity. The model was well validated and adequate.

Model	Main Model	Main Model + RE	Age + VL + Fever	VL + Fever	Age + VL	Age Only	VL Only
Δ DIC	reference	2.11	4.26	8.94	12.92	10.17	23.86
Parameters							
Coef. for Hazard from Community	0.70 (0.47, 0.99)	0.70 (0.45, 0.99)	0.71 (0.48, 1.00)	0.74 (0.50, 1.03)	0.73 (0.49, 1.03)	0.72 (0.49, 1.01)	0.76 (0.52, 1.07)
Hazard from Household	0.04 (0.02, 0.11)	0.03 (0.01, 0.08)	0.04 (0.01, 0.10)	0.08 (0.03, 0.17)	0.07 (0.02, 0.16)	0.07 (0.03, 0.15)	0.15 (0.07, 0.30)
Characteristics							
Factors affecting susceptibility:							
Age \leq 18 vs. Age 19 - 50	1.40 (0.95, 2.02)	1.42 (0.95, 2.07)	1.39 (0.93, 2.01)	1.29 (0.87, 1.85)	1.39 (0.94, 2.01)	1.41 (0.95, 2.04)	1.29 (0.87, 1.86)
Age > 50 vs. Age 19 - 50	0.38 (0.19, 0.66)	0.37 (0.18, 0.67)	0.37 (0.19, 0.67)	0.34 (0.17, 0.62)	0.37 (0.19, 0.66)	0.37 (0.19, 0.66)	0.33 (0.17, 0.59)
Vaccination	0.88 (0.50, 1.45)	0.88 (0.50, 1.48)	0.88 (0.51, 1.47)	0.86 (0.48, 1.43)	0.89 (0.50, 1.47)	0.89 (0.51, 1.45)	0.86 (0.50, 1.41)
Factors affecting infectivity:							
Age \leq 18 vs. Age > 18	2.89 (1.57, 6.73)	3.01 (1.61, 6.83)	2.74 (1.40, 6.55)	-	3.27 (1.59, 8.31)	3.88 (1.99, 9.36)	-
Antiviral	0.79 (0.51, 1.23)	0.77 (0.47, 1.23)	0.80 (0.52, 1.25)	0.81 (0.52, 1.26)	0.88 (0.56, 1.38)	0.87 (0.56, 1.34)	0.89 (0.57, 1.38)
Viral Load at symptom onset, Low Viral Load as reference:							
Medium Viral Load	-	-	1.00 (0.50, 2.07)	0.95 (0.48, 2.01)	0.95 (0.49, 1.91)	-	0.99 (0.48, 2.11)
High Viral Load	-	-	1.23 (0.68, 2.45)	1.58 (0.88, 3.14)	1.26 (0.70, 2.42)	-	1.86 (1.03, 3.62)
Virus Subtype, sH1N1 as reference:							
sH3N2	1.53 (0.93, 2.58)	1.49 (0.88, 2.66)	1.56 (0.97, 2.70)	1.40 (0.85, 2.39)	1.52 (0.92, 2.59)	1.52 (0.93, 2.62)	1.35 (0.82, 2.31)
pH1N1	0.98 (0.48, 1.86)	0.93 (0.42, 1.87)	1.02 (0.49, 2.03)	0.98 (0.47, 1.94)	0.97 (0.45, 1.95)	0.95 (0.43, 1.85)	0.92 (0.42, 1.81)
Unsubtypable A	1.00 (0.19, 2.77)	0.95 (0.18, 3.06)	1.05 (0.20, 3.03)	0.99 (0.15, 2.89)	1.11 (0.17, 3.33)	1.09 (0.20, 3.30)	1.01 (0.10, 3.08)
Fever	2.47 (1.39, 4.85)	2.58 (1.34, 5.78)	2.44 (1.33, 4.94)	2.86 (1.56, 6.29)	-	-	-

The baseline hazard of household transmission was 0.04 (95% credible interval (CrI): 0.02, 0.11), indicating a transmission probability of 3.92% (95% CrI: 1.98%, 10.42%). Age had significant effect on both susceptibility and infectivity. Elder adults over 50 years old were 62% less susceptible (95% CrI: 34%, 81%) than younger adults, and children under 18 years were nearly 3 times more infectious (189%, 95% CrI: 57%, 573%) than adults. Moreover, infected household members who had fever symptom were 147% more infectious (95% CrI: 39%, 385%). The model did not find any significant effect on household influenza transmission of vaccination, the use of antiviral and virus subtypes.

The random effect was then added on the main model, and the goodness-of-fit was not improved (Δ DIC = +2.11). By Kruskal-Wallis and Fisher's exact tests, we found that age, viral load and the onset of fever symptom were significantly mutually correlated. Therefore, in addition to the main model (including age and fever), we tried other combinations of these three factors affecting infectivity. Viral load was not a significant factor with the presence of age or fever, however, when age and fever were both removed, the effect of viral load became significant that high viral load household members were 86% more infectious (95% CrI: 3%, 262%) than low viral load ones.

Conclusion

Age and the onset of fever symptom were two factors could significantly affect household transmission of influenza A. Due to the correlation with age and fever, viral shedding could have significant effect on infectivity when age and fever were absent in the model. We did not find the significant effect of virus subtypes, vaccination or antiviral treatment.

References

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