Transmissibility of seasonal and pandemic influenza in a cohort of households in Hong Kong

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Seasonal and pandemic influenza

- Seasonal influenza viruses circulate every year, infect 5-20% of the population, cause mild illness in the majority of infected, and serious illness or death in a small minority.
  - Type A (subtypes H1N1 and H3N2) and type B viruses predominate.

Seasonal and pandemic influenza

- Seasonal influenza viruses circulate every year, infect 5-20% of the population, cause mild illness in the majority of infected, and serious illness or death in a small minority.
  - Type A (subtypes H1N1 and H3N2) and type B viruses predominate.
- Occasionally novel influenza A viruses emerge and lead to global pandemics with infection rates in the range 20-50%.
  - In 2009 the pH1N1 virus emerged in North America and rapidly spread around the world.
  - Valuable opportunity to study how the characteristics of a pandemic virus differ from seasonal viruses.

Influenza transmission in households?

- Many characteristics of influenza transmission remain poorly understood.
- Perhaps 30% of influenza transmission is thought to occur within the household (Ferguson, 2006, Nature; Chao, 2010, PLoS CB).
- One measure of transmissibility in households is the Secondary Attack Proportion – the probability that a susceptible individual will be infected by an index case in the same household.
- The household SAP for pH1N1 was estimated at 10-30% in the U.S. (Yang, 2009, Science; Cauchemez, 2009, NEJM).
- Is pH1N1 more transmissible than seasonal influenza?

Empirical studies of household transmission

We can recruit families after an initial index case has been identified and measure secondary transmission, in a case-ascertained design (Yang et al, 2006, Appl Stat).

- Advantage: An efficient design to estimate the in-home SAP.
- Disadvantage: Gives little information on the amount of infections resulting from contact with the community.
- Disadvantage: Possible selection bias associated with recruitment of index cases.

Case-ascertained study of household transmission during the pandemic

- Recruit index cases from outpatient clinics, use a rapid test to permit follow-up on a subset with confirmed influenza.
- Home visit usually arranged within 12 hours (max 36h).
- Nose and throat swabs from all household members at initial visit and after 3 and 6 days regardless of illness, to permit laboratory confirmation of secondary infections by RT-PCR.
- Blood draws on days 0 and 21-30 for serology in a subset.

Comparison of seasonal and pandemic influenza

Table: Secondary attack proportions in 94 households

Definition of influenza	Index cases with pandemic flu (n=41)		Index cases with seasonal flu (n=53)	
	SAR	(95% CI)	SAR	(95% CI)
RT-PCR	0.08	(0.03, 0.14)	0.09	(0.05, 0.15)
ARI†	0.26	(0.16, 0.36)	0.19	(0.12, 0.27)
ILI†	0.06	(0.03, 0.11)	0.04	(0.01, 0.07)

† ARI is at least 2 of fever$\geq$37.8°C, cough, headache, sore throat, aches or pains in muscles or joints. ILI is fever$\geq$37.8°C plus cough or sore throat.

- Comparative SAPs remained similar in subgroup analyses stratified by age.
- Further details in Cowling BJ et al. N Engl J Med 2010; 362:2175-84.

Cohort studies

Alternatively we can recruit a cohort of families before the influenza season and prospectively follow-up to observe primary and secondary infections.

- Advantage: Avoids potential bias due to selection of index cases.
- Advantage: Allows inference on the amount of infections resulting from contact with the community.
- Disadvantage: Possibly lower power to estimate SAP and household transmission parameters (cohort studies can require more resources).

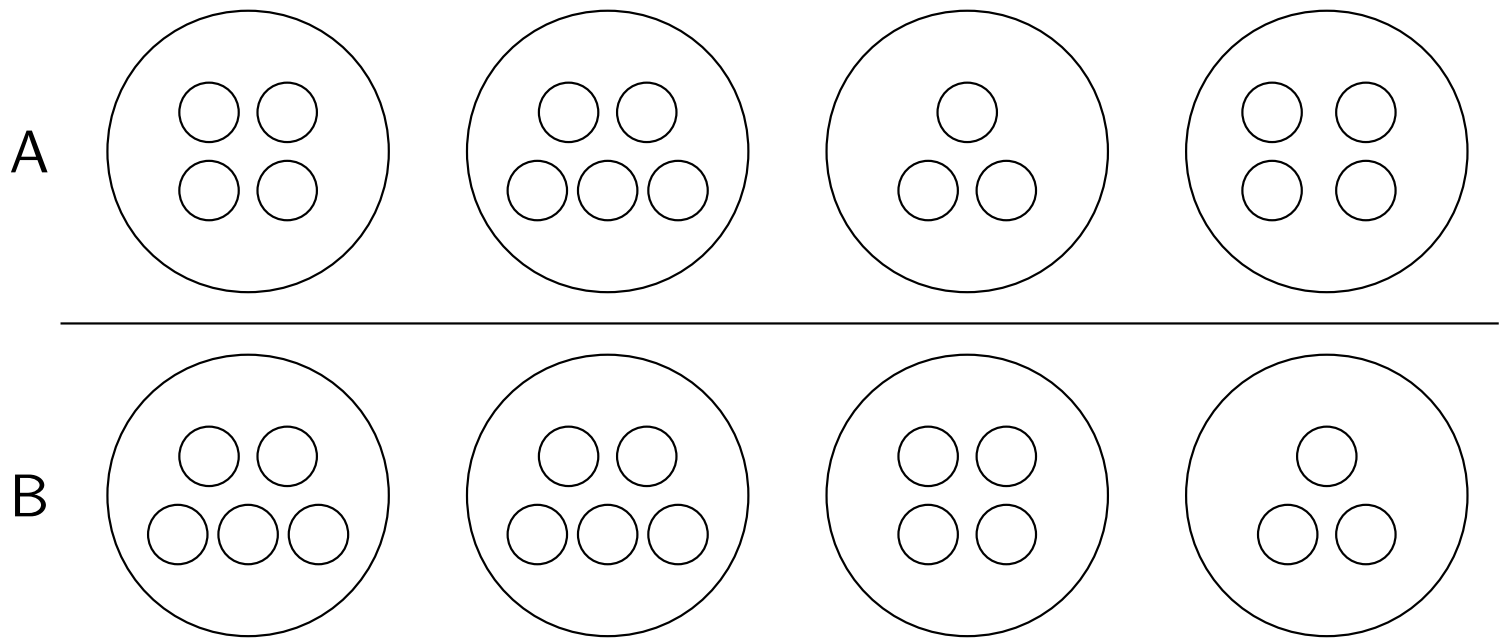
Analysis of infectious disease cohort studies

Known or partially known infection times. Usually results from symptom reports or laboratory confirmed infections from specimens collected during illness

Final outbreak size data. Usually result from the use of serological data which does not provide information about infection times (Longini, 1982, AJE).

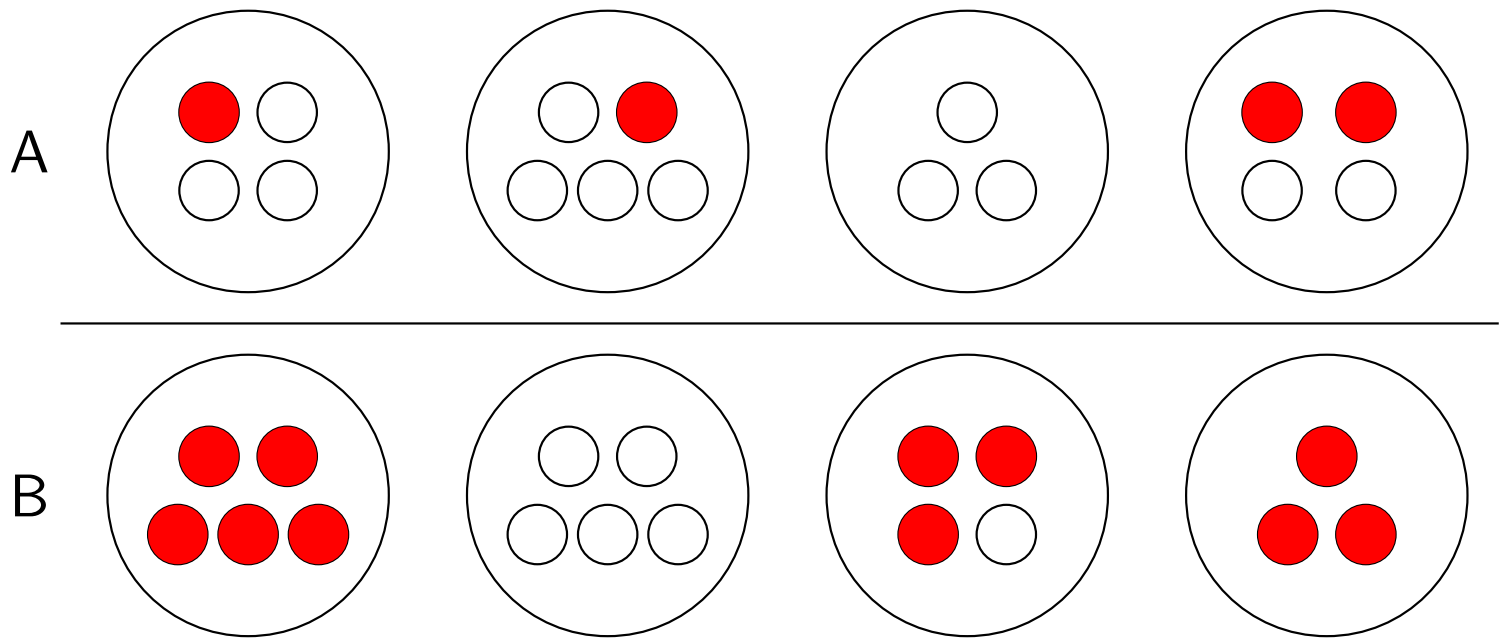
Final outbreak size data

At the start of an epidemic everyone is susceptible.



Final outbreak size data

At the end of an epidemic some people have been infected.



History of final outbreak size models

- In 1928 Soper proposed a model transmission of disease based on "the law of mass action".
- Lowell Reed and Wade Hampton Frost extended Soper's model to develop a simple stochastic chain binomial model for epidemics (Abbey 1952).
- Sugiyama (1960) extended the Reed-Frost model to incorporate in-home transmission.
- Longini and Koopman (1982) proposed a likelihood for a model assuming the Reed-Frost model for in-home transmission and some probability of external infection from the community.

- Ball (1997) showed that epidemics can take off even when the community reproductive number R_c, the number of people an infected person will infect outside their household, is considerably less than 1 if considerable transmission occurs within households.
- O'Neill (2000) demonstrated how the Longini-Koopman model can easily be incorporated into a Bayesian framework with MCMC.

Objectives

The objectives of our study are to:

- Estimate household transmission parameters for pandemic and seasonal influenza viruses from a cohort study.
- Extend existing models to incorporate separate parameters for adults and children.

Basic Longini-Koopman model

Assume that in a study population all individuals are disease susceptible, the infectious period is the same for all infected individuals and that after they are infected they will recover and no longer be infectious or susceptible to re-infection. Define

- q_c as the probability that an individual escapes infection from the community during the time period under study and
- q_h as the probability that an individual escapes infection given that another household member is infected.

Basic Longini-Koopman model (con't)

Assume we observe a family, denoted w_{js}, where j out of s susceptibles are infected during the period under study. Define $\alpha_{js} = Pr(W_{js} = w_{js}|q_c, q_h)$ and $\alpha_{00} = 1$. Then the likelihood for q_c and q_h is given by

$$L(q_c, q_h|w_{js}) = \binom{s}{j} \alpha_{jj} (q_c q_h^j)^{s-j}.$$

Basic Longini-Koopman model (con't)

Following the convention of Longini (1982, AJE) we define the

- Community Probability of Infection (CPI) as $1 - q_c$,
- Secondary Attack Proportion (SAP) as $1 - q_h$.

The SAP can be interpreted as the probability that a susceptible individual will be infected by another individual in the same household who has already been infected. The CPI can be interpreted as the probability of acquiring infection from the community during the period of study.

Model fitting

- Model fitted using MCMC.
- Used uniform priors for all parameters except for the CPI for sH1N1 among both children and adults, for which we specified a beta(1.5, 28.5) distribution based on estimates of plausible range of attack rates, due to the low number of seasonal H1N1 infections during our follow-up period.
- Used data augmentation to handle missing data.

Extension to account for age

We can classify children and adults separately and have two sets of escape probabilities for children and adults. C_c, C_h, A_c, A_h become the child and adult community and home escape probabilities respectively. The likelihood becomes

$$L(C_c, C_h, A_c, A_h | w_{ijst}) = \alpha_{ijij} \binom{s}{i} (C_c C_h^{i+j})^{s-i} \binom{t}{j} (A_c A_h^{i+j})^{t-j}.$$

where i out of s susceptible children and j out of t susceptible adults are infected.

Accounting for immunity

- The Longini-Koopman model assumes all subjects initially are disease susceptible.
- Some people appear to be immune to influenza, and higher serum antibody titers against a specific strain is correlated with immunity against that strain.
  - Some studies have found an antibody titer $\geq 1:40$ correlates with 50% protection against infection.
- We conducted analyses excluding individuals with higher antibody titers against the viruses in our study in an attempt to account for immunity.
  - Used thresholds of $> 1:40$ and $> 1:160$.

Cohort study

- Cluster-randomized (at household level), placebo-controlled, double-blind study.
- Original objective – to study the indirect benefits of influenza vaccination in households.
- Eligibility: Households including at least one child aged 6-18 who was not contraindicated against TIV.
- Pilot study: 2008-09 (119 households) – analyzed here.
- Main study: 2009-10 (796 households) – awaiting data.

Study design

- Households randomized into two arms, one child in each household received either
  1. One dose of trivalent inactivated influenza vaccine
  2. 0.5ml saline (placebo control)
- Sera collected from all household members at baseline, mid-study (+6m) and at the end of the study (+12m).
  - Sera also collected from vaccinees one month after vaccination.
- Daily symptom diaries and biweekly telephone calls; home visits triggered by at least two signs/symptoms of acute respiratory illness.

Pilot study timeline

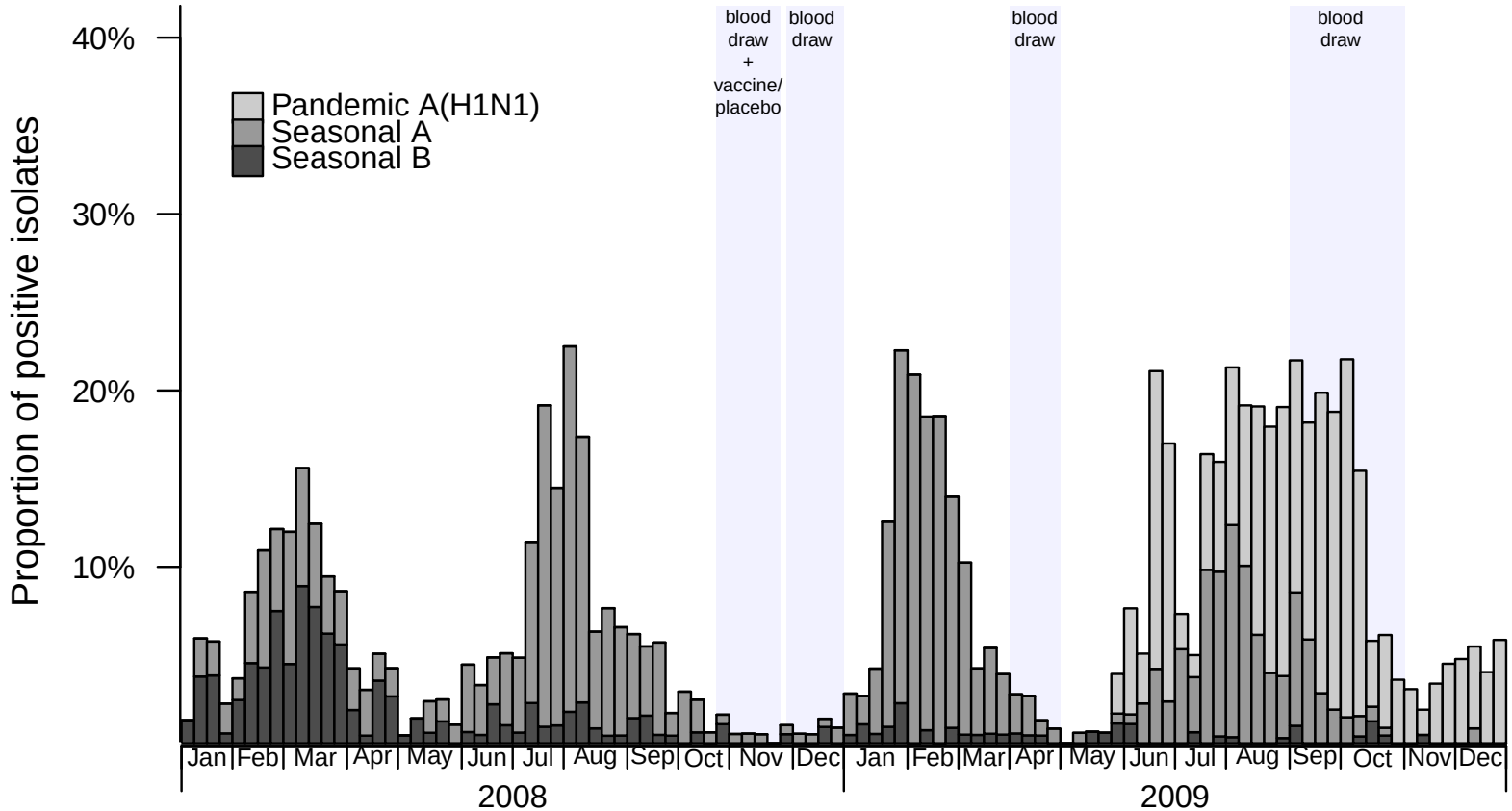


Figure: Study timeline versus local inpatient virological surveillance.

Current analyses focus on the period Apr 2009 through Sep-Oct 2009.

Influenza infection rates

Table: Cumulative incidence of infection in 423 individuals in 117 households, summer 2009.

	Children		Adults	
	Estimate	(95% CI)	Estimate	(95% CI)
Serologically confirmed influenza*				
pandemic A/H1N1	0.23	(0.17, 0.30)	0.08	(0.04, 0.12)
seasonal A/H1N1	0.06	(0.03, 0.11)	0.03	(0.01, 0.06)
seasonal A/H3N2	0.12	(0.07, 0.17)	0.06	(0.03, 0.10)
seasonal B†	0.02	(0.00, 0.05)	0.01	(0.00, 0.05)

* 4-fold or greater rise in antibody titre by HI (seasonal) or viral microneutralization (pandemic).

† We did not include seasonal B in further analyses because of the low infection rate in summer 2009.

Family sizes

		Adults				
		1	2	3	4	Total
Children	1	13	30	5	3	51
	2	9	41	4	2	56
	3	2	7	0	0	9
	4	0	1	0	0	1
	Total	24	79	9	5	117

Study included 423 individuals in 117 households; paired sera available from 376 (89%) participants.

Cross-reactions

- 12/376 (3%) individuals had 4-fold or greater antibody rises against more than one strain.
- Assuming only one infection is possible during the 4-6 month follow-up period, we classified the most likely infecting strain based on acute confirmation of infection (2), the highest geometric rise in titers (5), infections in other family members (2) and dates of reported illness episodes (3).
- Also conducted a sensitivity analysis allowing multiple infections during the period in those 12.

Estimates of CPI and SAP for all individuals

Table: CPI and SAP estimates in full dataset.

Type	Community probability of infection		Secondary attack proportion	
	Children (95% CI)	Adults (95% CI)	Children (95% CI)	Adults (95% CI)
pH1N1	0.15 (0.10, 0.21)	0.05 (0.02, 0.09)	0.23 (0.07, 0.38)	0.06 (0.00, 0.14)
sH1N1	0.03 (0.01, 0.05)	0.02 (0.01, 0.05)	0.06 (0.00, 0.24)	0.06 (0.00, 0.20)
sH3N2	0.09 (0.05, 0.14)	0.05 (0.02, 0.08)	0.06 (0.00, 0.19)	0.09 (0.01, 0.19)

Estimates accounting for immunity ($\leq 1:160$ susceptible)

Table: CPI and SAP estimates excluding 36-37% of children and 1-3% of adults who had antibody titers $> 1:160$ against sH1N1 and sH3N2.

Type	Community probability of infection		Secondary attack proportion	
	Children (95% CI)	Adults (95% CI)	Children (95% CI)	Adults (95% CI)
pH1N1	0.15 (0.11, 0.22)	0.05 (0.02, 0.09)	0.21 (0.07, 0.38)	0.06 (0.00, 0.15)
sH1N1	0.04 (0.01, 0.08)	0.02 (0.01, 0.05)	0.08 (0.00, 0.35)	0.06 (0.00, 0.23)
sH3N2	0.13 (0.08, 0.21)	0.05 (0.02, 0.09)	0.17 (0.00, 0.40)	0.10 (0.02, 0.23)

Estimates accounting for immunity ($\leq 1:40$ susceptible)

Table: CPI and SAP estimates excluding 60-61% of children and 7-10% of adults who had antibody titers $> 1:40$ against sH1N1 and sH3N2.

Type	Community probability of infection		Secondary attack proportion	
	Children (95% CI)	Adults (95% CI)	Children (95% CI)	Adults (95% CI)
pH1N1	0.16 (0.11, 0.22)	0.05 (0.02, 0.09)	0.22 (0.07, 0.37)	0.07 (0.00, 0.16)
sH1N1	0.06 (0.02, 0.11)	0.03 (0.01, 0.05)	0.15 (0.00, 0.50)	0.06 (0.00, 0.24)
sH3N2	0.16 (0.08, 0.26)	0.06 (0.03, 0.10)	0.30 (0.02, 0.61)	0.12 (0.02, 0.25)

Conclusions

- Our estimates of escape probabilities for seasonal and pandemic influenza seem comparable with other estimates in the literature, and suggest no substantial differences in transmissibility between seasonal and pandemic viruses after accounting for potential immunity.
- CPIs and SAPs were higher in children than adults.
- With regard to seasonal influenza A viruses, adjusting for prior immunity has a substantial impact on estimation of q_h and q_c.

Limitations

- Did not explicitly model effect of seasonal influenza vaccination, but vaccinated individuals typically had high titers against seasonal strains and would have been excluded in the models accounting for immunity.
  - 70% and 74% of the children who received vaccine had baseline titers $> 1:40$ against sH1N1 and sH3N2 respectively and thus were removed from at least one subgroup analysis.
- Imperfect sensitivity and specificity of serologic outcome as an indicator of infection.

Future Plans

- Ball (1997) noted that in a stochastic epidemic process q_c and q_h are not independent, i.e., $q_c = f(R_c, q_h)$. The Longini-Koopman model could be formulated to allow direct estimation of R_c and q_h.
- We have data indicating when some family members were infected (lab-confirmed acute infection), symptom diaries on most families, and for other families we only have final outcome data. How can this partial information be included?
- Allowing for imperfect serologic data (next talk . . .)

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THE END

Risk factors for pH1N1 in cohort study

Table: Factors affecting risk of pandemic H1N1 among all participants

	Lab-confirmed pH1N1*	
	AOR†	(95% CI)
Age (years)		
≤ 15	6.60	(2.17, 20.13)
$16 - 45$	2.53	(0.80, 7.99)
> 45	1.00	
Seasonal influenza during study‡	0.35	(0.14, 0.87)
Received 2008-09 seasonal TIV	1.11	(0.54, 2.26)

* 4-fold rise in antibody titre to A/CA/2009 or infection confirmed by RT-PCR

† Adjusted Odds Ratio also adjusted for sex and date of completion of study

‡ Seasonal influenza infection indicated by 4-fold rise in antibody titer or confirmed by RT-PCR

Household transmission study – SAP by age group

Definition of influenza	Index cases with pandemic flu		Index cases with seasonal flu	
	SAR	(95% CI)*	SAR	(95% CI)*
Index age ≤ 15	*(n=19)*		*(n=20)*	
RT-PCR	0.11	(0.02, 0.23)	0.13	(0.05, 0.24)
ARI†	0.33	(0.20, 0.47)	0.21	(0.09, 0.34)
ILI†	0.07	(0.02, 0.14)	0.05	(0.00, 0.10)

Household transmission study – SAP by age group

Definition of influenza	Index cases with pandemic flu		Index cases with seasonal flu	
	SAR	(95% CI)*	SAR	(95% CI)*
Index age ≤ 15	*(n=19)*		*(n=20)*	
RT-PCR	0.11	(0.02, 0.23)	0.13	(0.05, 0.24)
ARI†	0.33	(0.20, 0.47)	0.21	(0.09, 0.34)
ILI†	0.07	(0.02, 0.14)	0.05	(0.00, 0.10)
Index age > 15	*(n=22)*		*(n=33)*	
RT-PCR	0.05	(0.00, 0.11)	0.07	(0.02, 0.12)
ARI†	0.20	(0.08, 0.32)	0.17	(0.09, 0.27)
ILI†	0.05	(0.00, 0.11)	0.03	(0.00, 0.08)

* By the cluster bootstrap method.

† ARI is at least 2 of fever$\geq$37.8°C, cough, headache, sore throat, aches or pains in muscles or joints. ILI is fever$\geq$37.8°C plus cough or sore throat.

Secondary attack rates

Traditionally, household secondary attack rates (SAR) have been defined as

$$\text{SAR} = \frac{\text{No. of infected household members-1}}{\text{No. of susceptible household member-1}}$$

but Kemper (1980) and Longini (1982) point out that this estimate can be greatly biased due to co-primary infections, tertiary infections and non-sequential infections.

Proportion of infections acquired within households

Longini, Koopman (1982) suggest estimating the proportion of infections acquired in-home by

$$\frac{I - N(1 - q_c)}{I}$$

where I is the total number of infections and N is the total number of susceptible individuals.

	pandemic A(H1N1)	seasonal A(H1N1)	seasonal A(H3N2)
Proportion	0.18 (0, 0.38)	0.03 (0, 0.32)	0.13 (0, 0.35)

Model Fit

χ^2 goodness-of-fit tests

age structure	titres $\leq$	pandemic A(H1N1)	seasonal A
No	40	$\chi^2_6 = 3.9, p = 0.69$	$\chi^2_7 = 10.0, p = 0.20$
	160	$\chi^2_6 = 3.6, p = 0.73$	$\chi^2_6 = 1.3, p = 0.97$
	all	$\chi^2_9 = 7.5, p = 0.58$	$\chi^2_7 = 4.5, p = 0.73$
Yes	40	$\chi^2_7 = 2.4, p = 0.94$	$\chi^2_5 = 10.5, p = 0.06$
	160	$\chi^2_8 = 2.1, p = 0.98$	$\chi^2_9 = 4.6, p = 0.87$
	all	$\chi^2_{10} = 5.5, p = 0.86$	$\chi^2_8 = 6.9, p = 0.55$

Use in the literature–Seasonal Influenza

Influenza A(H1N1), A(H3N2) and influenza B from the Seattle and Tecumseh studies.

	1977-78 A(H3N2)	1978-79 A(H1N1)	1975-76 B
CPI	0.13	0.46	0.17
SAP	0.15	0.31	0.13

(Longini, 1982; Longini, 1984)

Clinical trial of virucidal nasal tissue (Longini and Monto, 1988)

Use in the literature–Pandemic Influenza

1957 Asian Influenza A (H2N2)

	Tokyo	Osaka
CPI	0.41	0.21
SAP	0.07	0.09

(Nishiuri and Chowell, 2007)