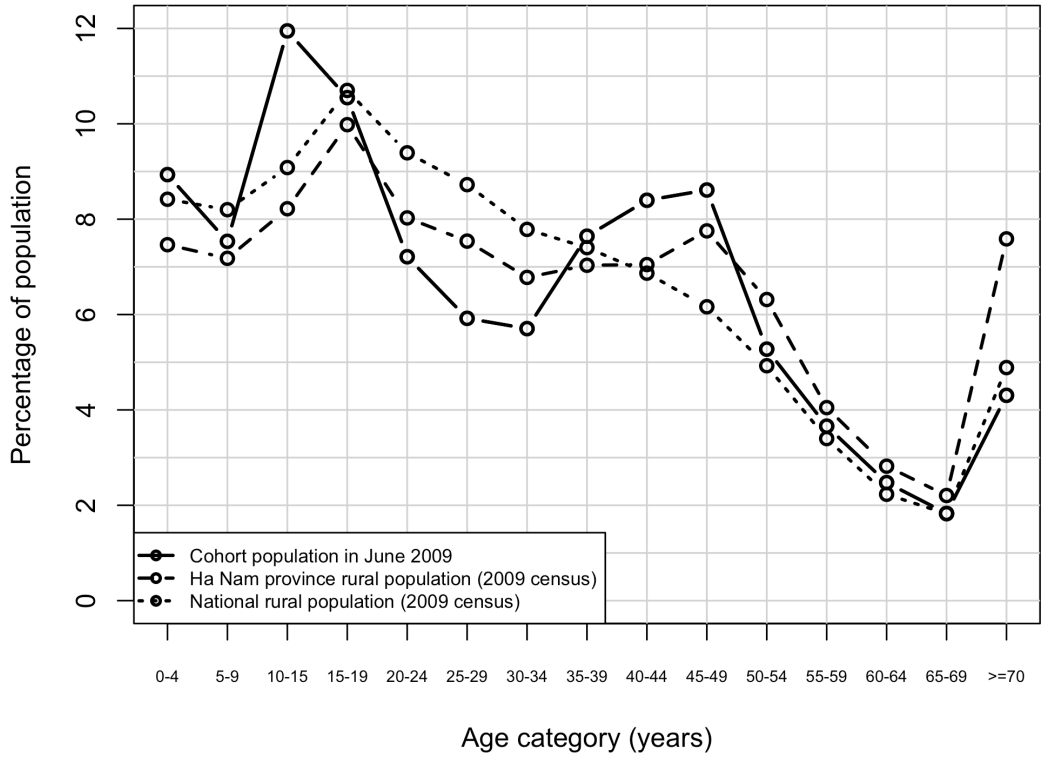
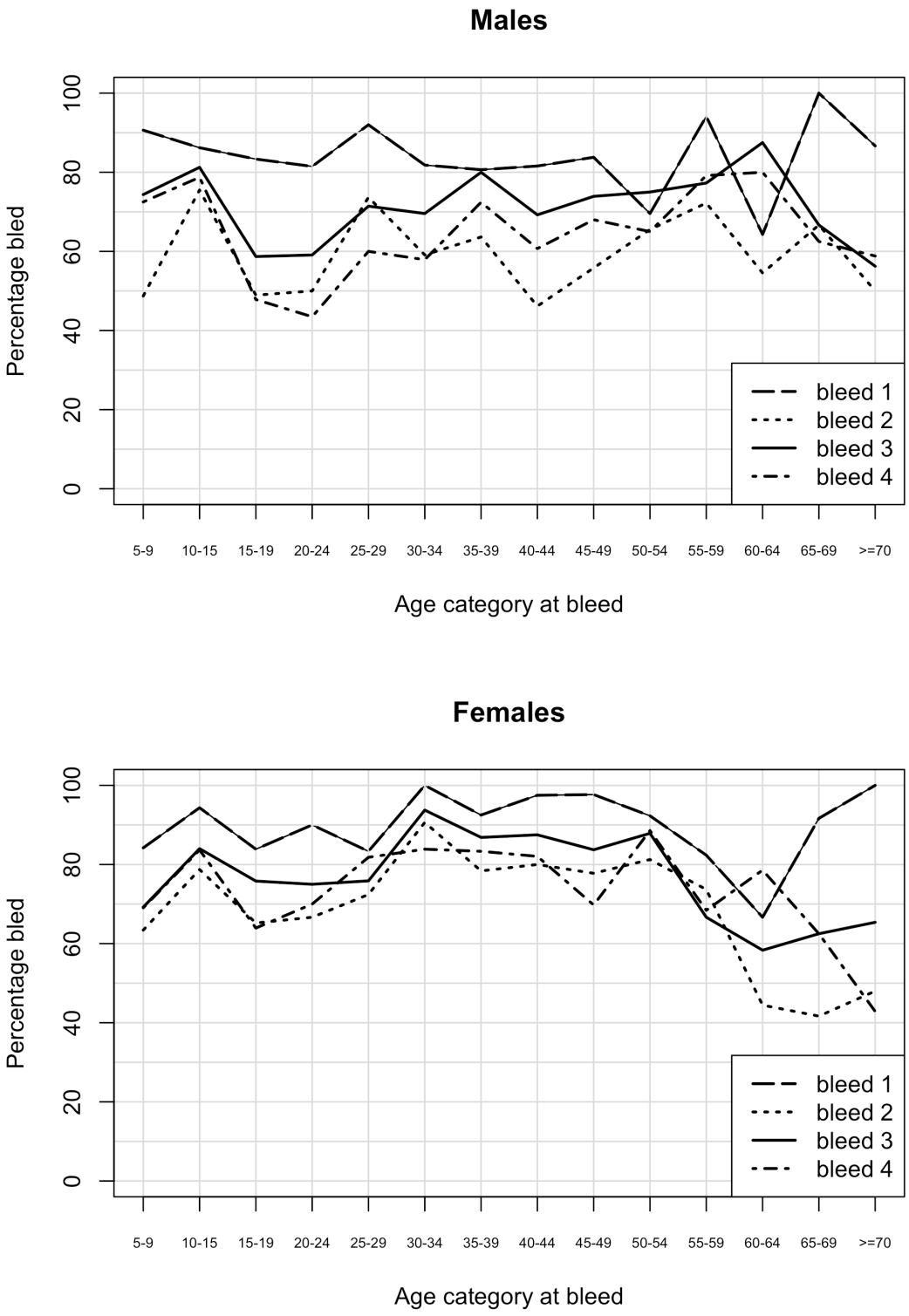
Web Appendix.

Web Figure 1. Age distribution of the cohort compared to provincial and national rural populations, Ha Nam, Vietnam, 2007-2010.

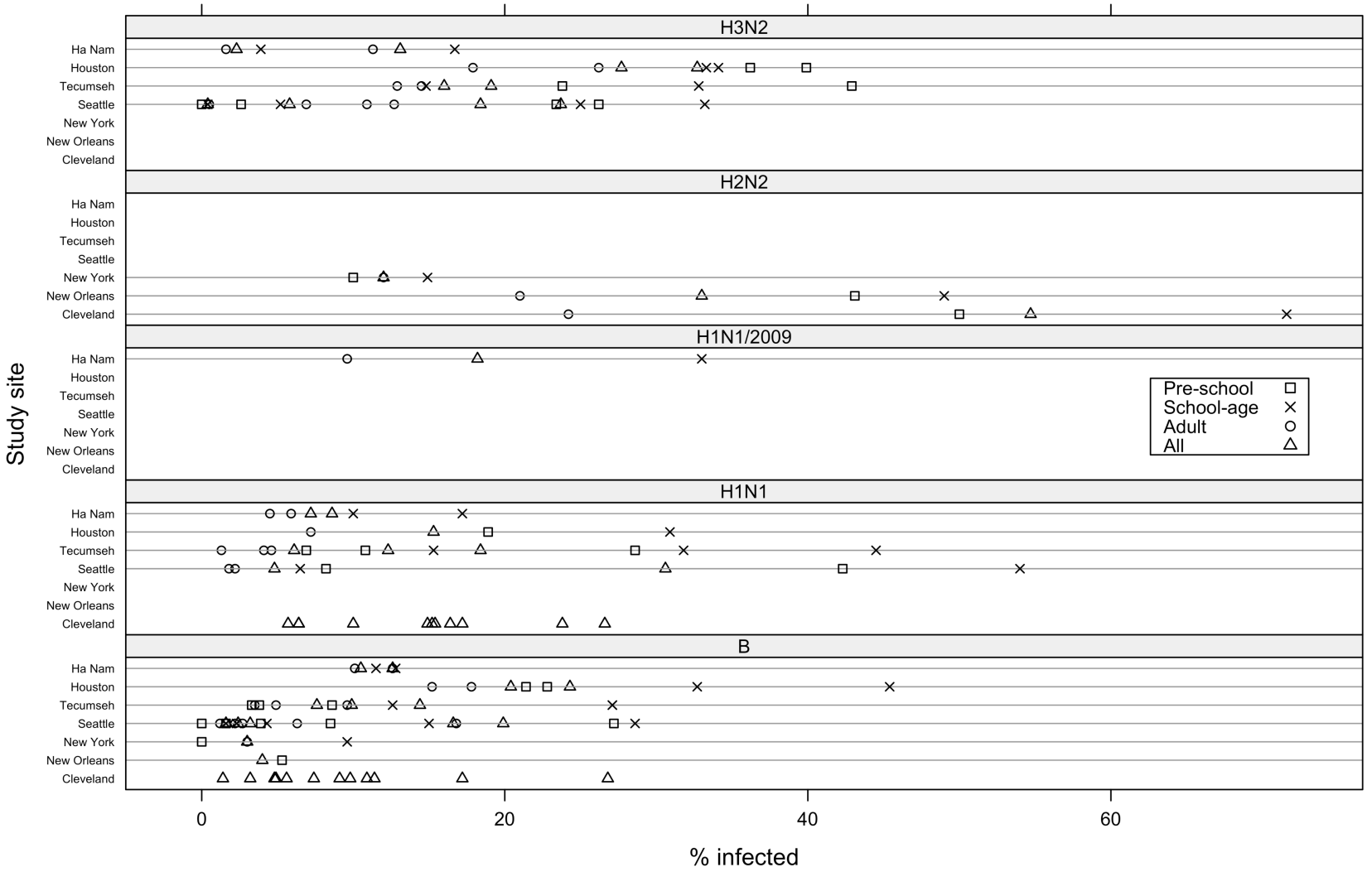


Age distribution of the cohort in June, 2009, compared to the age distribution of Ha Nam province and the national rural population as ascertained in the 2009 Population and Housing Census.

Web Figure 2. Frequency of bleeding amongst cohort participants under ILI surveillance, by age and gender. Ha Nam, Vietnam, 2007-2010.



Web Figure 3. Influenza infection rates in Ha Nam 2007-2010, compared to historic household cohort studies.



Data and data sources available in Web Table 1.

Web Table 1. Source data for Web Figure 3.

						Proportion infected by age group*				
Reference	**Study site**	**Year(s)**	**Type / subtype**	**Definition of infection**	**Outcome measure**	**Pre-school**	**School-age**	**Adult**	**All**	**Notes**
(4)	Cleveland	Fall 1947 - Spring 1948	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				15.2	
(4)	Cleveland	Spring 1948 - Fall 1948	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				17.2	
(4)	Cleveland	Fall 1948 - Spring 1949	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				16.4	
(4)	Cleveland	Spring 1949 - Fall 1949	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				15.4	
(4)	Cleveland	Fall 1949 - Spring 1950	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				14.9	
(4)	Cleveland	Spring 1950 - Fall 1950	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				6.4	
(4)	Cleveland	Fall 1950 - Spring 1951	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				23.8	
(4)	Cleveland	Spring 1951 - Fall 1951	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				6.4	
(4)	Cleveland	Fall 1951 - Spring 1952	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				10	
(4)	Cleveland	Spring 1952 - Fall 1952	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				5.7	
(4)	Cleveland	Fall 1952 - Spring 1953	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				26.6	
(4)	Cleveland	Spring 1953 - Fall 1953	H1N1	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				6.4	
(4)	Cleveland	Fall 1947 - Spring 1948	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				3.2	

(4)	Cleveland	Spring 1948 - Fall 1948	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				9.8	
(4)	Cleveland	Fall 1948 - Spring 1949	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				7.4	
(4)	Cleveland	Spring 1949 - Fall 1949	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				9.1	
(4)	Cleveland	Fall 1949 - Spring 1950	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				17.2	
(4)	Cleveland	Spring 1950 - Fall 1950	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				10.9	
(4)	Cleveland	Fall 1950 - Spring 1951	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				5.6	
(4)	Cleveland	Spring 1951 - Fall 1951	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				11.4	
(4)	Cleveland	Fall 1951 - Spring 1952	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				26.8	
(4)	Cleveland	Spring 1952 - Fall 1952	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				4.8	
(4)	Cleveland	Fall 1952 - Spring 1953	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				4.9	
(4)	Cleveland	Spring 1953 - Fall 1953	B	A 4-fold or greater rise in HI titer	% of persons with two samples taken at approximately six month intervals.				1.4	
(5)	Cleveland	1956-1957	H2N2	A 4-fold or greater rise in HI titer by CF or HI test, or both.	% of persons with 2 serum samples at approximately six month intervals, except for infants followed from birth whose first serum specimen at 12 to 18 months of age was taken to reflect their infection experience since birth.	50	71.6	24.2	54.7	Pandemic year
(6)	New York	1961-1965	H2N2	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	% of persons with 2 serum samples at approximately six month intervals (except infants)	10	14.9	12	12	

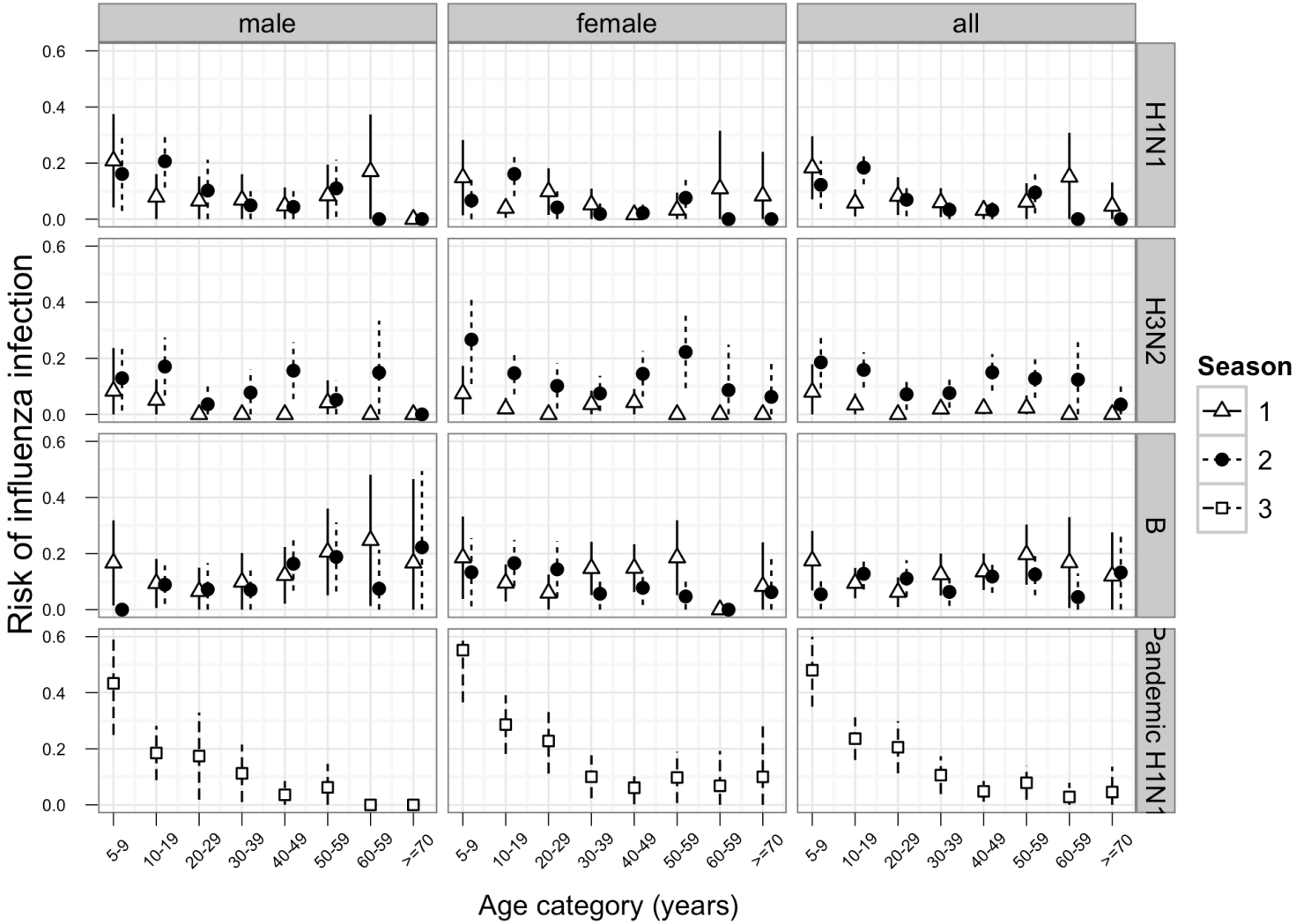
(6)	New Orleans	1956-1959	H2N2	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	% of persons with 2 serum samples at approximately six month intervals (except infants)	43.1	49	21	33	Pandemic year
(6)	New York	1961-1965	B	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	% of persons with 2 serum samples at approximately six month intervals (except infants)	0	9.6	3	3	
(6)	New Orleans	1956-1959	B	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	% of persons with 2 serum samples at approximately six month intervals (except infants)	5.3			4	
(7)	Seattle	1965-1969	A	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	Per 100-person years	25.5	18	14.1	18.6	0-<6 years and 6-19 years
(7)	Seattle	1965-1969	B	Seroconversion to positive or a 4-fold or greater rise in CF antibody titer	Per 100-person years	27.2	15	16.8	19.9	0-<6 years and 6-19 years
(8)	Seattle	1975-1976	H3N2	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	23.4	25	10.9	18.4	
(8)	Seattle	1976-1977	H3N2	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	2.6	5.2	6.9	5.8	
(8)	Seattle	1977-1978	H3N2	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	26.2	33.2	12.7	23.7	
(8)	Seattle	1978-1979	H3N2	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	0	0.4	0.5	0.4	
(8)	Seattle	1975-1976	B	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	8.5	28.6	6.3	16.6	
(8)	Seattle	1976-1977	B	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	3.9	1.6	1.2	1.6	
(8)	Seattle	1977-1978	B	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	1.6	4.3	2.2	3.2	
(8)	Seattle	1978-1979	B	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	0	2.3	2.7	2.4	
(8)	Seattle	1977-1978	H1N1	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	8.2	6.5	2.2	4.8	
(8)	Seattle	1978-1979	H1N1	Virus isolation or 4-fold or greater rise in CF or HI titer	% per season	42.3	54	1.8	30.6	Pandemic year
(9)	Tecumseh	1966-1971	A	A 4-fold or greater rises in HI titer or 1:16 titre in person with previously undetectable titre.	% per surveillance year	17.7	18.5	15	16.7	
(9)	Tecumseh	1966-1971	B	A 4-fold or greater rises in HI titer or 1:16 titre in person with previously undetectable titre.	% per surveillance year	3.3	12.6	4.9	7.6	
(10)	Tecumseh	1977-1978	H3N2	A 4-fold or greater rise in HI	% per outbreak period	42.9	32.8	12.9	19.1	Outbreak year

				titer or virus isolation						
(10)	Tecumseh	1980-1981	H3N2	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	23.8	14.8	14.5	16	Outbreak year
(10)	Tecumseh	1977-1978	H1N1	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	6.9	31.8	4.6	12.3	Outbreak year
(10)	Tecumseh	1978-1979	H1N1	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	28.6	44.5	4.1	18.4	Pandemic year
(10)	Tecumseh	1980-1981	H1N1	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	10.8	15.3	1.3	6.1	Outbreak year
(10)	Tecumseh	1976-1977	B	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	3.8	27.1	3.5	9.9	Outbreak year
(10)	Tecumseh	1979-1980	B	A 4-fold or greater rise in HI titer or virus isolation	% per outbreak period	8.6	27.1	9.6	14.4	Outbreak year
(11)	Houston	1976	H3N2	A 4-fold or greater rise in HI titer or virus isolation	% per between January 1975-April 1976.	36.2	33.3	17.9	27.7	Outbreak year
(12)	Houston	1976-1977	B	A 4-fold or greater rise in HI or microneutralization titer, or virus isolation.	% per epidemiologic year	22.8	45.4	17.8	24.3	Outbreak year
(12)	Houston	1979-1980	B	A 4-fold or greater rise in HI or microneutralization titer, or virus isolation.	% per epidemiologic year	21.4	32.7	15.2	20.4	Outbreak year
(13)	Houston	1977-1979 & 1980-1981	H1N1	A 4-fold or greater rise in HI or microneutralization titer, or virus isolation.	Per 100-person years	18.9	30.9	7.2	15.3	Outbreak years / 0-<6 years and 6-17 years
(13)	Houston	1977-1979 & 1980-1981	H3N2	A 4-fold or greater rise in HI or microneutralization titer, or virus isolation.	Per 100-person years	39.9	34.1	26.2	32.7	Outbreak years / 0-<6 years and 6-17 years
Horby	Ha Nam	2007-2008	H1N1	See main paper	Unadjusted % per season. See main paper		10	5.9	7.2	
Horby	Ha Nam	2007-2008	H3N2	See main paper	Unadjusted % per season. See main paper		3.9	1.6	2.3	
Horby	Ha Nam	2007-2008	B	See main paper	Unadjusted % per season. See main paper		12.8	12.6	12.6	
Horby	Ha Nam	2008-2009	H1N1	See main paper	Unadjusted % per season. See main paper		17.2	4.5	8.6	
Horby	Ha Nam	2008-2009	H3N2	See main paper	Unadjusted % per season. See main paper		16.7	11.3	13.1	
Horby	Ha Nam	2008-2009	B	See main paper	Unadjusted % per season. See main paper		11.5	10.1	10.5	
Horby	Ha Nam	2009-2010	H1N1/2009	See main paper	Unadjusted % per season. See main paper		33	9.6	18.2	Pandemic year

* Unless otherwise stated pre-school = 0-4 years; school-age = 5-19 years; adult ≥ 20 years

HI = Hemagglutination Inhibition assay. CF = Complement Fixation assay

Web Figure 4. Risk of influenza infection by season, influenza sub-type, gender, and age group. Ha Nam, Vietnam, 2007-2010.



Adjusted for household clustered design and standardized to age and gender distribution of the Vietnam national rural population aged ≥ 5years.

Full materials and methods

In 2007 a prospective, household-based community cohort was established in Thanh Ha Commune, Thanh Liem District, Ha Nam Province, Vietnam. Vietnam is a lower middle-income country that has achieved rapid economic growth since the economic reforms of the late 1980's. It has a population of 85.8 million (2009 census), making it the third most populous country in Southeast Asia and 13th in the world. Vietnam has a high population density (259 persons/km^2), with 70% of the population living in rural areas, and good health indicators for its level of development. Ha Nam Province is situated in the Northern Red River Delta of Vietnam, the most densely populated area of Vietnam (930 persons/km^2), about 60km south of the capital city Hanoi. At a latitude of 20.502034 decimal degrees and longitude 105.928642, Thanh Liem District has a tropical climate with an average monthly median temperature of 24.2°C, minimum monthly median 14.2°C, and a maximum monthly median of 33°C (2007-2008). The Province was selected on the basis of the availability of trained staff, the travelling distance from Hanoi, the prior circulation of influenza A/H5N1, and the quality of relationships with the implementing institute, the National Institute of Hygiene and Epidemiology (NIHE). Members of the Provincial Preventive Medicine Centre selected the study site following discussions with various sites about the willingness of the community to participate in the research. Thanh Ha Commune is a semi rural community with a population of 7,663 (2007), making a living mostly through mixed agriculture and small-scale production (e.g. embroidery). The Commune has a Health Centre and is divided administratively into seven hamlets, each with one or more hamlet health workers. A community consultation meeting was held to explain the purpose of the study to community members, elected representatives of the community, and representatives of community organizations.

The primary sampling unit of study was the household and all households in the Commune were eligible for inclusion in the study. A list of all households in the Commune was compiled from the local Government population register and was the source document for the selection of households for inclusion in the study. Households were randomly selected from the household list using a random number table. If a randomly selected household declined to participate, the next nearest

household was approached until a household was successfully recruited. All permanent residents in the household were eligible for inclusion and were requested to participate. All potential participants were given information on the purpose of the study, the associated risks and benefits, and were required to provide written informed consent before inclusion in the study. Parents or legal guardians provided written consent for participants aged less than 18 years.

Baseline variables

Households were recruited and baseline information collected during November and December 2007. Trained hamlet health workers (HHW) conducted face-to-face interviews with all participants. Individual participants provided information on date of birth; gender; ethnicity; occupation; contact with children at work or home; the number of children in the school and class (for participants of school age only); the presence of chronic disease; frequency of travel outside of the Commune, District, Province, and Country; influenza vaccination history; and smoking behavior. The nominated 'household head' provided information on the number of people living in the house; the familial relationship between household members; the number of rooms in the house; and the ownership of household assets.

Blood sampling

Participants aged 5 years and older (at time of sampling) were asked to provide blood at recruitment and at three further time points. Recruitment blood samples were drawn between 1st-7th December 2007 (bleed 1). Subsequent bleeds took place between 9th-15th December 2008 (bleed 2), 2nd-4th June 2009 (bleed 3), and on the 3rd April 2010 (bleed 4). The bleeding time points were not decided *a priori* but were chosen when national influenza surveillance data indicated that influenza circulation was minimal. The four sets of samples provided three sets of paired sera. Sodium heparin blood collection tubes were used for bleeds 1-3 in order that peripheral blood mononuclear cells (PBMCs) could be extracted for a sub-study on T-cell responses in influenza; sodium heparin tubes provided plasma for determining haemagglutination inhibiting (HI) antibody titres. DNA was extracted from the cell pellet of the heparin blood samples for a sub-study of host genetic influences on influenza infection. Bleed 4 used clot-activator serum tubes, which provide serum for determining HI antibody titres.

Influenza-like illness surveillance

Trained HHWs undertook weekly active surveillance of each participating household for episodes of influenza-like illness (ILI) and for changes in household composition. Participants were also encouraged to actively report any episode of ILI as soon as possible directly to the HHW. ILI was defined as 'as an illness with oral temperature of 38°C or more and either a cough or a sore throat'. All participating households were provided with an alcohol-in-glass clinical thermometer and informed of the definition of an ILI used in the study. Any participant reporting an ILI was asked to attend the Commune Health Centre where a trained member of the health centre staff would take a nose swab and a throat swab for storage in viral transport media at 2-4 °C pending transfer to the laboratory for testing. Synthetic tipped swabs with plastic shafts were used and placed in 3 ml of transport media (DMEM with 2% v/v BSA, 0.3% v/v NaHCO3 and antibiotics). Participants whom reported an ILI were asked to complete a 10-day symptom diary.

Definition of exposure and outcome variables

For the purpose of analysis, an influenza 'season' was defined as the period between consecutive bleeds, and an influenza 'transmission period' was defined as the period when influenza was known to be circulating on the basis of RT-PCR confirmed clinical cases.

'Influenza infection' was defined as either the detection of influenza RNA in a swab sample by reverse transcription polymerase chain reaction (RT-PCR) or a four fold or greater rise in HI antibody titre in paired sera, with the second titre at least 1:40. If paired sera were not available, a single high titre of at least 1:160 for seasonal influenza, or a titre of ≥ 1:80 in someone aged under 40 years for pandemic influenza H1N1, was also considered to indicate recent 'influenza infection'.

'Influenza illness' was defined as the detection of influenza-specific RNA in a swab by RT-PCR and the reporting of an ILI, or serological evidence of recent influenza infection (see above) plus an ILI episode occurring during a known period of transmission of the relevant influenza subtype. For linking serological evidence of recent influenza A infection to specific ILI episodes, the following influenza A 'transmission periods' were defined: 01/07/2008-30/09/2008 (influenza transmission

period 1), 01/04/2009-05/06/2009 (influenza transmission period 2); and 01/09/2009-31/12/2009 (influenza transmission period 3). Influenza B circulated throughout 2008 and a 'transmission period' could not be defined, therefore serological evidence of recent influenza B infection was putatively linked to any ILI episode that was not attributable to influenza A infection.

Laboratory methods - reverse transcription polymerase chain reaction (RT-PCR) assay

Detection of influenza viruses in nasal- and throat-swab specimens was performed using either conventional or real-time RT-PCR. The real-time assay was performed according to the U.S. CDC/WHO protocols (CDC reference no. I-007-05, Accessed November 30, 2009, at http://www.who.int/csr/resources/publications/swineflu/CDCRealtimeRTPCR_SwineH1Assay-2009_20090430.pdf.). Conventional RT-PCR assays for H1N1/2009 were performed according to WHO Protocols using primers M30F2/08 and M264R3/08 for influenza A matrix and NIID-swH1 Conv-F1 and NIID-swH1 Conv-R1 for H1N1/2009 (WHO information for laboratory diagnosis of pandemic H1N1/2009 virus in humans – revised. 23 November 2009 (http://www3.ha.org.hk/idctc/document/swineflu/WHO_Diagnostic_RecommendationsH1N1_20090521.pdf). Conventional RT-PCR for seasonal influenza strains was preformed using one-step reactions with primers for influenza A matrix (as above); H3N2 (forward AAGCATTCCYAATGACAAACC, reverse ATTGCRCCRAATATGCCTCTAGT); H1N1 (forward AGGCAAATGGAAATCTAATAGCGC, reverse CCATTGGTGCATTTGAGGTGATG); and influenza B (forward TCCTCAACTCACTCTTCGAGCG, reverse CGGTGCTCT TGACCAAATTGG).

Laboratory methods - hemagglutination inhibition (HI) assay

Influenza hemagglutination inhibition (HI) assays were performed according to standard protocols.. Virus stocks used as antigens were cultured from swabs from select study participants with positive RT-PCR assays for each subtype in each season, except for season 3 where the WHO reference strain A/H1N1/California/7/2009-like was used. They were either propagated in the

allantoic cavities of 10-day-old embryonated hen's eggs or in MDCK cells. Virus concentrations were determined by haemagglutination (HA) assay titration with appropriate erythrocytes at 0.5% (v/v) and used at titres of 1:8. Each virus was initially tested in HA with erythrocytes from chickens, guinea pigs and turkeys, and erythrocytes from chicken were selected for 2008 H1N1 (2008), and from turkey for H3N2 and H1N1/2009. Participant and reference serum or plasma was treated with receptor destroying enzyme (Denka Seiken, Japan), heat inactivated then adsorbed against packed appropriate erythrocytes. HI assays were performed in U-bottom 96-well microtitre plates with 0.5% v/v appropriate erythrocytes. Cell controls and positive controls containing WHO reference sera for each strain were included with each batch of sera tested and two sera controls were included for each participant. Paired sera were tested together in the same assay run.

Serum/plasma samples were tested at an initial dilution of 1:10 and then at two-fold serial dilutions to a maximum dilution of 1:1280. Results were accepted if sera and cell controls provided the correct non-agglutinated pattern and if positive controls were within two-fold of anticipated/historical titres. Samples that were negative by HI assay in the lowest dilution (1:10) were assigned a titre of 1:5 for the purposes of computing seroconversion.

Study size

The Tecumseh study of respiratory illness in the community estimated influenza virus associated illness occurred at a rate of around 220 per 1000 population per year with an additional 50 to 100 asymptomatic but serologically confirmed infections (1). Assuming an incidence rate of influenza infection of around 20% per influenza season and ignoring potential household clustering of influenza illness, a total of 1000 recruited subjects would lead to a two-sided 95% confidence interval for the incidence with a precision (width) of 5%.

Handling of quantitative variables in the analysis

The age of participants at the start of each influenza season was calculated from their date of birth. For analysis and presentation of data on ILI episodes and RT-PCR confirmed influenza infection, age was grouped into four categories to ensure sufficient outcome events in each category: 0-<5 years, 5-<20 years, 20-<40 years,

≥40 years. The same categories (except for <5 years olds which were not asked to provide blood) were used for the analysis of data on risk factors for influenza infection. For graphical presentation of serological outcomes, we used a finer age resolution with the following categories: 0-<5, 5-<10, 10-<20, 20-<30, 30-<40, 40-<50, 50-<60, 60-<70, ≥70. Home crowding was defined as being present if there were more than 2 people per room.

Statistical methods

Absolute observed risks of ILI (for subjects under ILI surveillance) and of influenza infection (overall and for influenza subtypes, for subjects under influenza infection surveillance) were calculated per season. Participants were considered under ILI surveillance for a particular season if they were under weekly ILI surveillance throughout the influenza transmission period and they were considered under influenza infection surveillance if they additionally contributed a post-season blood sample. Absolute risks per season were preferred to rates (events per person time) as the incidence of influenza varies strongly over time. For example, while the time from bleed 1 to bleed 2 (season 1) was one year and the time from bleed 2 to bleed 3 (season 2) only 6 months, both seasons contained a full transmission period of both influenza H1N1 and H3N2.

Survey analysis methodology was used to derive risk estimates and associated 95% confidence intervals in the full population and in age subgroups. This provides valid inference accounting for effects of the survey design, which was based on cluster sampling by household. The inclusion of subjects for assessment of influenza infection required blood samples and the willingness to provide blood differed by age and gender. To correct for this sampling bias, and to provide results that can be generalized to the broader population, the influenza risk estimates were standardized to the age and gender structure of the Vietnamese rural population based on the 2009 Population and Housing Census. As children under 5 years of age were not asked to give blood samples, standardization for influenza risks was to the census population aged ≥5 years. Standardization was implemented by raking, i.e. post-stratification on the target age and gender distribution in turn until convergence (2).

Seven potential risk factors for influenza infection were pre-defined. To assess these factors, data were pooled over all three seasons and the overall risk of an influenza infection was modeled with a logistic mixed effects model depending on the season, a random household effect (to account for potential clustering within households), a random subject effect (to account for potential within-subject correlation between seasons) and the respective risk factors. The analysis was repeated for each influenza subtype separately.

All analyses were performed with the statistical software R 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria) and the companion R packages survey 3.22-3 (for survey sampling) and lme4 0.999375-35 (for mixed models) (3).

Missing data and loss to follow-up

Participants were excluded from all analyses if data on age or sex were missing. Participants were excluded from analysis of a particular influenza season if they were absent from the study site for a period of one week or more during the influenza transmission period; this included absence due to death, permanent out-migration, or temporary absence.

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