Influenza virus infections in Hong Kong in 2013-14: a community-based longitudinal seroepidemiological study

BJ Cowling *, JSM Peiris, KO Kwok

KEY MESSAGES

1. We conducted a longitudinal serologic study and estimated that between 3% to 7% of unvaccinated people in Hong Kong were infected in each of four influenza epidemics in 2013 and 2014.
2. Incidence of influenza virus infections was relatively low in children, in contrast to the very high incidence of infections reported in the 2009 pandemic.

Hong Kong Med J 2019;25(Suppl 7):S23-6
HMRF project number: 13120732

BJ Cowling, JSM Peiris, KO Kwok

School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong

* Principal applicant and corresponding author: bcowling@hku.hk

Introduction

Influenza viruses are responsible for a considerable disease burden every year including hundreds of excess deaths and thousands of excess hospitalisations in Hong Kong.[1,2] When considering the impact of influenza epidemics, it is important to distinguish the incidence of infections from the severity of infections. In typical influenza epidemics, the highest incidence of infection usually occurs in school-age children,[3] whereas the severity of infections generally increases with age, with elderly people having a higher risk of death than adults or children.[4]

Many population-based serologic studies have been conducted during influenza pandemics to infer the cumulative incidence of infection with the new strain, which is referred to as the attack rate.[5,6] We conducted a longitudinal serologic study in Hong Kong in 2009-10 and estimated that in the first wave of the H1N1pdm09 pandemic the cumulative incidence of infection was 39% (31%-49%) for persons 3-19 years, 8.9% (5.3%-14.7%) for persons 20-39 years, 5.3% (3.5%-8.0%) for persons 40-59 years, and 0.77% (0.18%-4.2%) for persons 60 years or older.[7]

However, few serologic studies have been conducted for interpandemic influenza.[8] A community-based study in the United Kingdom included an average of 1000 persons in follow-up for 5 consecutive years, with a smaller number of participants in the initial years and a large number during 2009-10.[9] An average of 18% of people were infected with influenza each winter in the United Kingdom, with a particularly high incidence of H1N1pdm09 in children during 2009-10.[9]

The current study aimed to: (1) estimate the age-specific attack rate of influenza A and B in a representative group of households using three sets of paired serology between November 2012 and February 2015, and (2) evaluate the risk factors for influenza virus infection including age and vaccination status.

Methods

We previously had conducted a longitudinal study in the general community by collecting sera at regular intervals to investigate serologic evidence of influenza virus infection and estimated the cumulative incidence of infections across epidemics and across years.[10] The current study was a 2-year extension of that longitudinal study, covering periods of influenza activity in 2013 and 2014.

The longitudinal study was initiated in July 2009 in the early stages of the first wave of pandemic influenza A(H1N1)pdm09. We recruited participants from the general population across Hong Kong via random-digit dialling and from a subset of respondents in an earlier telephone survey that was also conducted with random-digit dialling.[7] In November 2009, a second study round was conducted by inviting all individuals who joined the previous round to take part again. Individuals who did not join the first round but were living with a round 1 participant were also eligible to join. These two study rounds constitute the first phase of this study (rounds 1-2). The second phase of this study involved three subsequent study rounds with the same design (rounds 3-5). The third phase of the study was the basis of the present project and began on 6 December 2013. All participants in the existing cohort were invited to continue. The target sample size was maintained by replacing dropouts with new participants using the same recruitment approach (ie, telephone survey sampling).

All participants who provided serum samples must be ≥2 years old and Hong Kong residents who reside in Hong Kong for ≥5 days a week. All household contacts of the participants must reside with the participants for ≥5 days a week in the same household. Priority was given to households with members participating in previous rounds. Participants were invited to visit the study clinic in Kowloon to provide blood samples. The rationale for the study was explained and written informed consent obtained. For children aged 8 to 17 years, written consent was obtained from both the child and their parent or guardian. For children aged 2 to 7 years, written consent was obtained from the parent or guardian. A blood sample of 4 mL was collected in a clotted blood tube, and basic demographics and relevant medical history including vaccination history were recorded on a standardised form.

TABLE 1. Baseline characteristics of participants in 2012-2014*

	2011 census	Round 5 (November 2012 to March 2013) [n=920]	Round 6 (December 2013 to March 2014) [n=846]	Round 7 (from October 2014 to January 2015) [n=855]
Number of households	-	613	576	611
Mean household size	2.88	3.08	2.86	2.83
Age, y				
0-9	7.2	8 (0.9)	10 (1.2)	3 (0.4)
10-19	11.1	43 (4.7)	44 (5.2)	46 (5.4)
20-39	13.2	82 (8.9)	69 (8.2)	83 (9.7)
30-39	14.7	62 (6.7)	62 (7.3)	56 (6.5)
40-49	17.3	163 (17.7)	130 (15.4)	113 (13.2)
50-59	16.7	277 (30.1)	248 (29.3)	246 (28.8)
60-69	9.4	192 (20.9)	179 (21.2)	198 (23.2)
≥70	10.4	90 (9.8)	99 (11.7)	109 (12.7)
Missing	0.0	3 (0.3)	5 (0.6)	1 (0.1)
Sex				
Female	51.6	553 (60.1)	507 (59.9)	345 (40.4)
Male	48.4	367 (39.9)	335 (39.6)	509 (59.5)
Missing	0.0	0 (0.0)	4 (0.5)	1 (0.1)
Occupation†				
Category 1	-	189 (20.5)	126 (14.9)	155 (18.1)
Category 2	-	217 (23.6)	222 (26.2)	235 (27.5)
Category 3	-	410 (44.6)	391 (46.2)	386 (45.1)
Category 4	-	97 (10.5)	79 (9.3)	76 (8.9)
Missing	-	7 (0.8)	28 (3.3)	3 (0.4)
Chronic disease				
Yes	-	422 (45.9)	387 (45.7)	363 (42.5)
No	-	488 (53.0)	455 (53.8)	492 (57.5)
Missing	-	10 (1.1)	4 (0.5)	0 (0.0)
Ever smoke				
Yes	-	141 (15.3)	79 (9.3)	91 (10.6)
No	-	763 (82.9)	759 (89.7)	764 (89.4)
Missing	-	16 (1.7)	8 (0.9)	0 (0.0)
Receipt of vaccination in prior session				
Yes	-	152 (16.5)	179 (21.2)	183 (21.4)
No	-	748 (81.3)	648 (76.6)	600 (70.2)
Missing	-	20 (2.2)	19 (2.2)	172 (8.4)

* Data are presented as % or No. (%) of participants unless otherwise stated

† Category 1 denotes managers and administrators, professionals and associate professionals; Category 2 clerks, service workers and shop sales workers, craft and related workers, plant and machine operators and assemblers, elementary occupations; skilled agricultural and fishery workers; and occupations not classifiable; Category 3, housekeepers, retired, economically inactive, and maid; Category 4, students

The haemagglutination inhibition assay was used to identify titre level of influenza strains in the serum samples. A/California/7/2009 (H1N1) and B/Brisbane/60/2007 (B/Victoria lineage) were tested antigens in rounds 5-7. Round 5 specimens were additionally tested for A/Perth/16/2009 (H3N2) and specimens from rounds 1-5 were additionally tested for A/Victoria/361/2011 (H3N2).

An infection was defined as a four-fold rise in antibody titres measured by the haemagglutination inhibition assay between consecutive serum samples. We estimated the cumulative incidence of infections indicated by serology in defined epidemics of particular influenza types/subtypes in 2013 and 2014. Cumulative incidence was estimated for four age-groups, and age-standardised estimates were made using the population distribution in the 2011 census. Logistic regression models were used to estimate odds ratio of new influenza virus infections versus different baseline characteristics.

Results

Of 920 participants in round 5, 629 (68%) extended the follow-up period to round 6 (from December 2013 to March 2014). In addition, 131 brand-new individuals and 86 participants from previous rounds other than round 5 were recruited in round 6, with a total of 846 participants. In round 7 from October 2014 to January 2015, 855 participants (587 from round 6, 191 new top-ups, and 77 old top-ups) were recruited. For rounds 5-7, we obtained 2621 serum samples from 1355 individuals.

Compared with the 2011 census, our study cohort over-sampled older adults (aged ≥50 years) and under-sampled younger individuals. Participants had similar baseline characteristics. The self-reported vaccination coverage ranged from 16% to 21% across three study rounds, and middle-aged adults or older adults reported vaccination most commonly (Table 1).

Of 12 distinct influenza epidemics identified from 2009 to 2014, five (epidemic number 8-12) were captured by our study period: the A(H3N2) epidemic in July to October 2013, the A(H3N2) epidemic in

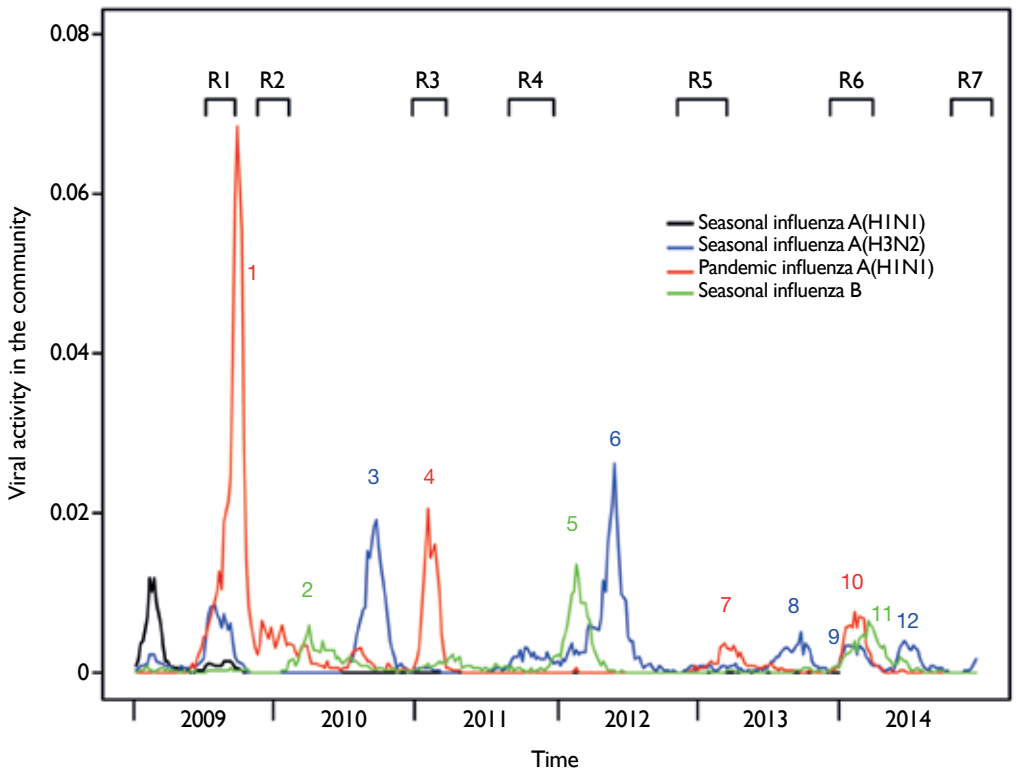

FIG. Study timeline and the community virus activity from 2009 to 2016

TABLE 2. Incidence of influenza virus infections confirmed by serology in different epidemics. The main circulating virus in each epidemic is highlighted in bold. Preference is given to subsequent study rounds that (almost) neatly bracket the epidemics. Study round selection is only eligible to epidemics of unique subtype between two subsequent study rounds.

Epidemic No.	Epidemic	Study rounds involved	Incidence (95% confidence interval) of influenza virus infection confirmed by serology		
			A/California/7/2009	A/Victoria/361/2011	B/Brisbane/60/2007
8	A(H3N2)	5,6	0.14 (0.12-0.17)	**0.11 (0.08-0.13)**	0.01 (0.01-0.02)
9	A(H3N2)*	-	-	-	-
10	H1N1pdm09	5,7	**0.10 (0.07-0.13)**	0.08 (0.06-0.11)	0.04 (0.02-0.06)
11	B	5,7	0.10 (0.07-0.13)	0.08 (0.06-0.11)	**0.04 (0.02-0.06)**
12	A(H3N2)	6,7	0.05 (0.04-0.07)	0.05 (0.04-0.07)	0.04 (0.02-0.05)

* This epidemic was bracketed by study rounds that were also surrounded by epidemics of the same subtype (ie, epidemic number 8 and 12).

TABLE 3. Age-specific and age-standard incidence estimates for the main circulating virus strain in each epidemic

	Incidence (95% confidence interval)			
	A/Victoria/361/2011 for epidemic 8	A/California/7/2009 for epidemic 10	B/Brisbane/60/2007 for epidemic 11	A/Victoria/361/2011 for epidemic 12
Age-group, y				
0-19	0.03 (-0.03 to 0.09)	0.00 (0.00 to 0.00)	0.04 (-0.04 to 0.12)	0.16 (0.03 to 0.29)
20-39	0.05 (0.00 to 0.10)	0.07 (0.00 to 0.13)	0.05 (-0.01 to 0.11)	0.06 (0.00 to 0.11)
40-59	0.05 (0.02 to 0.08)	0.05 (0.02 to 0.07)	0.01 (0.00 to 0.02)	0.03 (0.01 to 0.05)
≥60	0.05 (0.01 to 0.09)	0.06 (0.01 to 0.11)	0.05 (0.00 to 0.10)	0.05 (0.01 to 0.09)
Age-standardised to the 2011 population of Hong Kong	0.05	0.05	0.03	0.07

December 2013 to March 2014, the H1N1pdm09 epidemic in January to March 2014, the B epidemic in January to May 2014, and the A(H3N2) epidemic in June to July 2014 (Fig).

Proxied by the proportion of four-fold seroconversion to A/Victoria/361/2011, the new incidence attributable to the epidemic number 8 was 0.11 (95% confidence interval [CI]=0.08–0.13), whereas that to epidemic number 12 was 0.05 (95% CI=0.04-0.07) [Table 2]. The incidence of epidemic number 9 was not estimated because it was bracketed by study rounds that were also surrounded by epidemics of the same subtype. Age-specific and age-standard incidence estimates among unvaccinated individuals were calculated for the main circulating virus in each epidemic (Table 3). The incidence of new cases among older adults (aged ≥60 years) were similar across different epidemics (0.05-0.06). On the contrary, the incidence of new cases among young age groups (aged ≤19 years) was much more for epidemic number 12 (0.16) than other epidemics. Age and presence of chronic diseases were significant risk factors, whereas baseline H1N1 titre was significantly protective against subsequent H1N1 infection.

Discussion

Five epidemics were identified from 2013 to 2014. In our cohort, the overall incidence of infections was about 5% to 11% for influenza A epidemics and about 4% for influenza B epidemics during 2013-2014. Incidence was relatively low in children, in contrast to the very high incidence of infections reported in the 2009 pandemic.[7,11]

Age and chronic diseases were significantly associated with the risk of infection. Pre-existing baseline antibody titres were protective for A(H1N1), which has remained antigenically similar for a number of years, but not for A(H3N2) which has experienced much more antigenic drift.

This study has some limitations. The rounds of sera collection did not neatly bracket each epidemic, and we were unable to estimate the incidence of epidemic number 9. Models that account for individual titre boosting and waning to address non-bracketing issue are in development.[12] The four-fold rise in antibody titres across a prolonged period as an indicator of an influenza virus infection does not have perfect sensitivity and specificity for a true infection event because of waning in titres over time, temporal fluctuations in antibody titre for reasons not related to infection events, and the limitations in haemagglutination inhibition assays. In addition, we did not account for clustering in the analysis, which would have slightly widened the confidence intervals.

Acknowledgement

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#13120732).

References

1. Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. J Infect Dis 2012;206:1862-71.
2. Li CK, Choi BC, Wong TW. Influenza-related deaths and hospitalizations in Hong Kong: a subtropical area. Public Health 2006;120:517-24.
3. Wu JT, Cowling BJ, Lau EH, et al. School closure and mitigation of pandemic (H1N1) 2009, Hong Kong. Emerg Infect Dis 2010;16:538-41.
4. Wu JT, Ma ES, Lee CK, et al. The infection attack rate and severity of 2009 pandemic H1N1 influenza in Hong Kong. Clin Infect Dis 2010;51:1184-91.
5. Kelly H, Peck HA, Laurie KL, Wu P, Nishiura H, Cowling BJ. The age-specific cumulative incidence of infection with pandemic influenza H1N1 2009 was similar in various countries prior to vaccination. PLoS One 2011;6:e21828.
6. Van Kerkhove MD, Hirve S, Koukounari A, Mounts AW; H1N1pdm serology working group. Estimating age-specific cumulative incidence for the 2009 influenza pandemic: a meta-analysis of A(H1N1)pdm09 serological studies from 19 countries. Influenza Other Respir Viruses 2013;7:872-86.
7. Riley S, Kwok KO, Wu KM, et al. Epidemiological characteristics of 2009 (H1N1) pandemic influenza based on paired sera from a longitudinal community cohort study. PLoS Med 2011;8:e1000442.
8. Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev 1994;16:351-73.
9. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med 2014;2:445-54.
10. Horby PW, Laurie KL, Cowling BJ, et al. CONSISE statement on the reporting of Seroepidemiologic Studies for influenza (ROSES-I statement): an extension of the STROBE statement. Influenza Other Respir Viruses 2017;11:2-14.
11. Wu JT, Ho A, Ma ES, et al. Estimating infection attack rates and severity in real time during an influenza pandemic: analysis of serial cross-sectional serologic surveillance data. PLoS Med 2011;8:e1001103.
12. Tsang TK, Fang VJ, Perera RA, et al. Interpreting seroepidemiologic studies of influenza in a context of nonbracketing sera. Epidemiology 2016;27:152-8.