

The epidemiological and public health research response to 2009 pandemic influenza A(H1N1): experiences from Hong Kong

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In recent years, Hong Kong has invested in research infrastructure to appropriately respond to novel infectious disease epidemics. Research from Hong Kong made a strong contribution to the international response to the 2009 influenza A (H1N1) pandemic (pH1N1). Summarizing, describing, and reviewing Hong Kong's response to the 2009 pandemic, this article aimed to identify key elements of a real-time research response. A systematic search in PubMed and EMBASE for research into the infection dynamics and natural history, impact, or control of pH1N1 in Hong Kong. Eligible articles were analyzed according to their scope. Fifty-five articles were included in the review. Transmissibility of pH1N1 was similar in Hong Kong to elsewhere, and only a small fraction

of infections were associated with severe disease. School closures were effective in reducing pH1N1 transmission, oseltamivir was effective for treatment of severe cases while convalescent plasma therapy has the potential to mitigate future pandemics. There was a rapid and comprehensive research response to pH1N1 in Hong Kong, providing important information on the epidemiology of the novel virus with relevance internationally as well as locally. The scientific knowledge gained through these detailed studies of pH1N1 is now being used to revise and update pandemic plans. The experiences of the research response in Hong Kong could provide a template for the research response to future emerging and reemerging disease epidemics.

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Introduction

The emergence of the 2009 influenza A(H1N1) pandemic (pH1N1) and the rapid global spread in 2009 was surprising for a number of reasons.¹ The pandemic virus came from a reassortment event in swine rather than birds, was a strain of H1N1 rather than a subtype that was not concurrently circulating in humans, and appeared to have a mild severity profile similar to seasonal influenza. Furthermore, the pandemic emerged in North America, whereas most attention had been focused on the risk of a novel virus emerging in south-east Asia.^{2,3}

Hong Kong, a subtropical city on the south coast of China, has been identified with influenza research for decades; indeed, the 1968 pandemic influenza A(H3N2) virus was named after the city after being first identified there in July 1968.⁴ Hong Kong has found itself on the front lines of recent emerging infectious disease outbreaks, including the first human outbreak of highly pathogenic avian influenza A(H5N1) in 1997,⁵ and the severe acute respiratory syn-

drome (SARS) outbreak from 2002–2003, which spread from southern China through Hong Kong to the rest of the world. Following SARS, the Centre for Health Protection was established to take a leading role in the prevention and control of diseases in Hong Kong. In 2004, the Hong Kong Government created the Research Fund for the Control of Infectious Diseases with an endowment of US\$57 million, aiming to encourage, facilitate, and support research on the prevention, treatment, and control of infectious diseases.

The population of Hong Kong have on one hand been sensitized to the risk of emerging infectious diseases through these experiences in the last 15 years, while Hong Kong's close connectivity to China and south-east Asia has led to fears that it may be one of the first developed cities affected by a novel pathogen such as a new pandemic influenza strain that emerges in the region.³ As a result, Hong Kong has invested heavily in infrastructure in preparation for future epidemics and pandemics. There has also been substantial investment in research infrastructure, essential to guide evidence-based policy locally as well as

internationally. Following the World Health Organization (WHO) global alert in April 2009, Hong Kong health authorities initially operated under containment efforts, including entry screening at airports, ports and border crossings, hospital isolation of cases, tracing and quarantine of contacts, and routine antiviral prophylaxis. Once the first local case was identified on June 11, Hong Kong transitioned to mitigation efforts, with greater attention to public health promotion of preventive measures. All kindergartens and primary schools were closed from June 12 until summer vacation in early July, while 43 secondary schools were closed after 1 or more confirmed case was identified. Incidence peaked in September, and the first wave petered out by early November. Confirmed pH1N1 infection was a notifiable disease throughout the first wave. Figure 1 summarizes a timeline of the first wave of pH1N1 in Hong Kong.

Here, we review the epidemiological and public health research response to pH1N1 in Hong Kong. Summarizing, describing, and reviewing the Hong Kong's response to the 2009 pandemic, this article aimed to identify key elements of the successful real-time research response. In particular, we consider some of the factors that facilitated a rapid and comprehensive research response to pH1N1 that could be a potential template for the research response in other countries.

Methods

Search strategy

Studies were retrieved from the electronic databases PubMed and EMBASE on April 19, 2012. We used the following free text search terms (<influenza> OR <flu> OR <pH1N1> OR <nH1N1> OR <pandemic> in 'Title/Abstract') AND (<Hong Kong> in 'Title/Abstract' or 'Affiliation') to identify studies on pH1N1 in Hong Kong. We also limited the search to articles published after the WHO issued the first alert on the novel H1N1 virus (April 24, 2009). Therefore, we included papers that were published within 3 years of the identification of pH1N1. Other relevant studies identified by the authors were manually retrieved.

Study selection

All titles of the papers identified by the search strategy were independently screened by two authors (P. W. and B.J.C.). Abstracts (plus full text) of manuscripts with potentially relevant titles (abstracts) were reviewed for eligibility. Articles were considered as eligible when falling under one or more of three following categories of interest: (i) studies on the epidemiological dynamics and clinical course of infection with pH1N1, including transmission, severity, risk

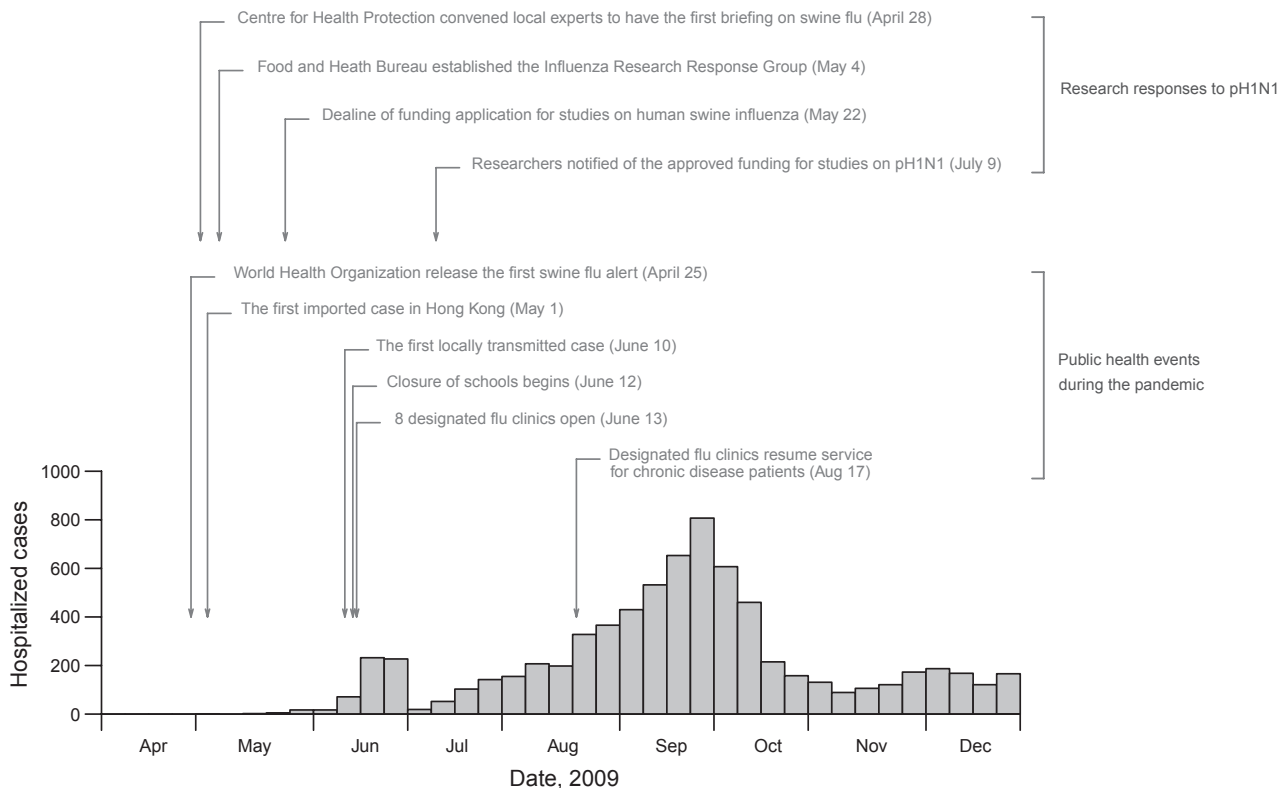


Figure 1. Timeline of the response to pH1N1 in Hong Kong versus the weekly numbers of hospitalizations of confirmed pH1N1 cases during the first wave, April–December 2009.

factors, and clinical features; (ii) studies on clinical, economic, or psychosocial impact of pH1N1; and (iii) studies on pharmaceutical and non-pharmaceutical interventions against pH1N1.

Data extraction

Details of the included studies were examined to identify the focal interests of research, the study design and the data used in the study, and the key findings of the study were extracted. The studies were analyzed according to the categories listed above. Articles could be included in more than one category. Based on the data, we enumerated essential components of findings that were independently covered in Hong Kong through its own epidemiological studies.

Results

Three hundred and seventy-six titles were identified through the database search. Of the 85 articles assessed for inclusion after examining the abstracts, we excluded 30 articles, which belong to case reports, commentaries, views, reviews, studies on genetics, or duplicate studies. Fifty-five full-length articles were finally included in this review (Figure 2). Articles relevant to infection dynamics and natural history, impact, or control are listed in Tables 1–3, respectively. All of the studies were conducted by first authors whose primary affiliation was an institute in Hong Kong. All studies were supported by local funding, including 32 (58%) that were supported by the Research Fund for the Control of Infectious Diseases. In addition, 13 (24%) studies acknowledged funding from international sources.

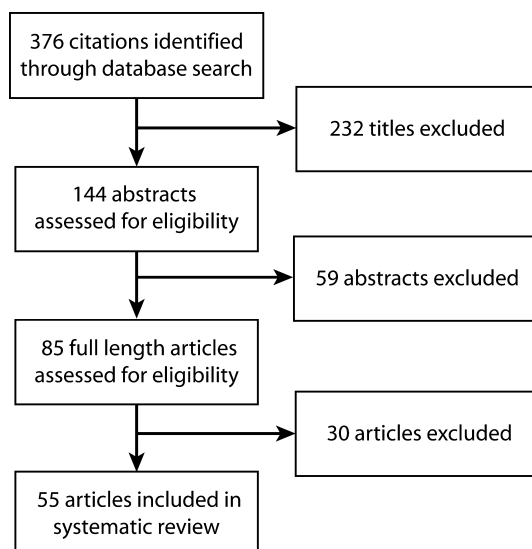


Figure 2. Flow chart of the study selection process.

Epidemiology of pH1N1

Of the 22 studies investigating pH1N1 infection dynamics and natural history, 14 described the epidemic dynamics of pH1N1 transmission,^{6–19} three examined the risk of infection and/or severity of the disease,^{20–22} and five studies assessed clinical features of pH1N1 infection^{23–27} (Table 1).

The initial effective reproduction number was estimated to decrease from around 1.4–1.5 at the start of the epidemic to around one during the school closures and summer vacations based on patterns in the incidence of confirmed cases and hospitalizations.^{9,10} Geographical clustering of confirmed cases was observed.^{14–16}

The risk of confirmed secondary pH1N1 infection among household contacts of 65 confirmed index cases was estimated at around 6% in a contact investigation of a school outbreak of pH1N1.¹³ Another household transmission study found that the risk of confirmed secondary pH1N1 infection was similar for pH1N1 and seasonal influenza in 99 households.¹⁸ Children appeared to be more susceptible to infection¹³ and more infectious than adults.¹⁸ Similarity in household transmissibility of pH1N1 and seasonal influenza was also observed in a prospective household cohort study during the pandemic.¹² Seasonal influenza and pH1N1 had similar patterns of viral shedding,¹⁸ clinical presentation,²⁵ and risk of admission to an intensive care unit (ICU) and death,²⁴ while hospitalized patients with pH1N1 infection tended to be younger and have higher mortality rates and higher frequency of complications,²¹ with different patterns of preexisting risk factors of severe disease.²⁴ One small case-control study could not confirm whether serum immunoglobulin G2 deficiency was a risk factor for severe infection.²⁰

A series of serologic studies were conducted in Hong Kong to estimate the cumulative incidence of infection through the course of the first wave.^{7,8,11,19,26} These studies indicated that about half of all children and 10–15% of the population had been infected with pH1N1 during the first wave of the pandemic. In combination with data on the number of hospitalizations, ICU admissions, and deaths associated with confirmed pH1N1, these serologic studies were also used to infer the severity profile of pH1N1 infection. While only around 10 and 1 per 100 000 infections were associated with admission to ICU or death in children, respectively, the risk of severe disease increased substantially with age to 220 per 100 000 in those aged 60 years or older.^{7,19} Serologic surveillance has the potential to provide timely estimates of transmissibility and severity in the next pandemic.⁸ A serologic study found similar seroprevalence among healthcare workers compared with the general community,²² while another study estimated similar risk of confirmed pH1N1 infection among clinical

Table 1. Summary of studies on the epidemiology of 2009 pandemic influenza A(H1N1) in Hong Kong

First author	Study period	Scope of study	Sample/Data and sample size	Study design	Key epidemiological findings
L Yang (6)	Jan 1998–Dec 2009	Transmission and severity	Cause-specific deaths	Ecological study	127 all-cause excess deaths were associated with pH1N1. The excess mortality rates associated with pH1N1 were highest in the elderly
JT Wu (7)	Apr–Dec 2009	Transmission and severity	Serum specimens: Blood donors: 12217 Hospital outpatients: 2520 Subjects from community: 917	Cross-sectional study	Around half of school-age children were infected during the first wave of pH1N1, and older adults had higher risk of ICU admission and death, compared with school-age children
JT Wu (8)	Apr–Dec 2009	Transmission and severity	Serum specimens: Blood donors: 12217 Hospital outpatients: 2520 Subjects from community: 917	Cross-sectional study	Serial cross-sectional serologic and clinical surveillance data can be applied to make reliable real-time estimates of the cumulative incidence of infection and severity early in the next pandemic
JT Wu (9)	May–Aug 2009	Transmission	All laboratory-confirmed pH1N1 infections in Hong Kong	Ecological study	The effective reproduction number was 1.6–1.7 at the start of the epidemic. More transmission occurred among children
BJ Cowling (10)	May–Nov 2009	Transmission	All laboratory-confirmed pH1N1 infections in Hong Kong	Ecological study	The effective reproduction number declined from 1.4–1.5 at the start of the local epidemic to 1.1–1.2 later in the summer in 2009
AIX Zhang (11)	May 2009–Feb 2010	Transmission and severity	Serum specimens: Baseline: 795 Pandemic: 1000 Laboratory-confirmed cases: 27116	Cross-sectional study	Individuals in 51–60 years of age group had the highest incidence of infection and incidence rate of severe disease
B Klick (12)	Apr–Oct 2009	Household transmission	Paired sera from members of 117 households	Cohort study	Risk of secondary infections in household contacts was similar for pandemic and seasonal influenza
YH Leung (13)	Jun 2009	Household transmission	Exposed students: 511 Infected students: 65 Household contacts: 205	Observational study	The risk of secondary infections was estimated to be 5.9% through a contact investigation of index cases identified in a school outbreak, and younger contacts (<18 year) and contacts without receiving oseltamivir prophylaxis were more likely to be infected
SS Lee (14)	May–Jul 2009	Geographic transmission	All laboratory-confirmed pandemic influenza cases during the study period in Hong Kong: 3675	Ecological study	Confirmed cases of pH1N1 occurred in geographical clusters and most transmission occurred in children
SS Lee (15)	May–Sep 2009	Geographic transmission	All laboratory-confirmed pandemic influenza cases during the study period in Hong Kong: 24414	Ecological study	Confirmed cases of pH1N1 occurred in geographical clusters

Table 1. (Continued)

First author	Study period	Scope of study	Sample/Data and sample size	Study design	Key epidemiological findings
SS Lee (16)	May–Sep 2009	Geographic transmission	All laboratory-confirmed pandemic influenza cases during the study period in Hong Kong: 24415	Ecological study	Confirmed cases of pH1N1 occurred in geographical clusters
WH Seto (17)	Jun 2009–May 2010	Nosocomial transmission	All notified pH1N1 cases among healthcare workers: 1158	Ecological study	Clinical and non-clinical healthcare workers had a similar risk of pH1N1 infection
BJ Cowling (18)	Jul–Aug 2009	Transmission and clinical profile	Index cases: 348 QuickVue test (+): 148 Household of the index: 99 Paired serum samples: 770	Cohort study	pH1N1 has similar characteristics to seasonal influenza viruses in terms of viral shedding, clinical illness, and household transmission. Around half of school-age children were infected during the first wave of pH1N1, and older adults had higher risk of ICU admission and death, compared with school-age children
S Riley (19)	Jul 2009–Feb 2010	Transmission and severity		Cohort study	It could not be determined whether IgG2 deficiency was a risk factor for severe pH1N1 infection
JFW Chan (20)	May 2009–Jan 2010	Risk factors of severe cases	Severe cases: 38 Mild cases: 36	Case–control study	Hospitalized adult patients infected with pandemic influenza were younger, but had higher mortality and risk of developing complications than those with seasonal influenza
N Lee (21)	Jun 2009–May 2010	Severity and risk factors	PCR confirmed adult inpatients (>16 year) with pH1N1 infection: 382	Case–control study	Occupational exposures in the hospital setting might not lead to higher risk of pandemic influenza infection in healthcare workers
Y Zhou (22)	Feb–Mar 2010	Risk of infection	Serum samples from healthcare workers: 703	Cross-sectional study	Younger age was associated with prolonged viral shedding in the respiratory tract and higher viral load in stool samples
KKW To (23)	Apr–Jun 2009	Clinical features	Case: 22 patients with pH1N1 infection Control: 44 patients with seasonal influenza infection	Case–control study	Hospitalized patients with pandemic influenza infection had similar risk of ICU admission and death, but presented different clinical features, compared with those infected with seasonal influenza
KKW To (24)	Jun–Oct 2009	Severity and clinical features	Laboratory-confirmed Pandemic influenza patients: 186 Seasonal influenza patients: 69	Case–control study	
SS Chiu (25)	Jul–Sep 2009	Clinical features	Child inpatients with pH1N1 infection: 99 Historical controls: 198 Concurrent control: 37	Case–control study	Hospitalized pediatric inpatients with confirmed pandemic and seasonal influenza had similar mild clinical manifestation

Table 1. (Continued)

First author	Study period	Scope of study	Sample/Data and sample size	Study design	Key epidemiological findings
GC Mak (26)	May 2009–Jan 2010	Population-level immunity Individual-level serologic response	Cross-sectional: Pre-pandemic: 234 sera Post-pandemic: 178 sera Case-control: Case: 246 Control: 52	Cross-sectional and case-control study	Previous exposure to heterologous viruses may provide cross-reacting antibody against the pandemic influenza. Patients with severe clinical presentations generally had stronger and higher humoral antibody responses than milder cases
T Lei (27)		Serologic study	Cross-sectional: Vaccinated healthy individuals: 60 paired sera (pre-/post-vaccination) Pandemic influenza patients: 23 post-infection sera Post-vaccination GBS patients: 8 sera Animal experiment: 6 mice	Cross-sectional study and animal challenge experiment	Vaccination against 2009 H1N1 virus was unlikely associated with the production of anti-ganglioside antibodies implicated in the pathogenesis of GBS. GBS associated with influenza infection or vaccination might be pathologically different from GBS preceded by an infection with <i>Campylobacter jejuni</i> or other pathogens

and non-clinical healthcare workers after adjustment for age.¹⁷ A small serologic study did not find evidence of the induction of anti-ganglioside antibodies by influenza viruses or vaccines.²⁷

Impact of pH1N1

Among the 27 studies describing the impact of pH1N1, six reported the clinical impact,^{6–8,10,11,19} 20 investigated psychological and/or behavioral responses to pH1N1 infection,^{28–47} and one study reported changes in the dynamics of circulating respiratory viruses potentially caused by the emergence of pH1N1⁴⁸ (Table 2). No studies were identified that investigated the economic impact of pH1N1. During the first wave in Hong Kong between April and December 2009, there were 7508 hospitalizations, 148 ICU admissions, and 63 deaths associated with pH1N1.^{7,8,10,11,19} One study estimated that there were 127 excess deaths associated with pH1N1, approximately double the number of deaths of confirmed cases.⁶

In the early stage of the pandemic, the local population generally did not perceive pH1N1 infection to be a threat nor estimate a high possibility of having a local outbreak.³¹ In another serial cross-sectional study, the perceived susceptibility to and severity of pH1N1 infection were fairly stable.³⁰ Avoidance behaviors, such as hand washing, mask wearing, or social distance, had been taken by many respondents since the beginning of the pandemic,^{30,32–34} while social distancing measures declined in its frequency through the course of the first wave.³⁰ Preventive measures taken by the population against the pandemic were dependent on a variety of factors, such as knowledge about the virus³⁰ and the efficacy and adverse effects of protective measures,^{44,46} perceived risk of infection,⁴⁵ trust in formal/informal information about pH1N1,³⁷ and previous experiences with avian influenza and SARS.²⁹

A study conducted in July 2009 reported reasonable acceptability of the pH1N1 vaccine, with around 50% of survey respondents reporting intention to receive pH1N1 vaccine for free, declining to 15% if the cost of the vaccine was higher than US\$25.^{41,42} The government subsequently ordered 3 million doses of pH1N1 vaccine for the local population of 7 million, and began distribution in December 2009. However, pH1N1 vaccine uptake was low, with <250 000 doses administered mainly to the elderly and healthcare workers. A subsequent longitudinal study found that intention to receive vaccine was an unreliable predictor of subsequent vaccine uptake.⁴⁴

Among healthcare workers, a study conducted in May 2009 found around 50% of survey respondents willing to receive pH1N1 vaccine.⁴⁵ Another study of community nurses in June 2009 found only 27% reporting willingness to receive pH1N1 vaccine.⁴⁰ Uptake of the monovalent pH1N1 vaccine was associated with previous seasonal

Table 2. Summary of studies on the impact of 2009 pandemic influenza A(H1N1) in Hong Kong

First author	Study period	Scope of study	Sample/data and sample size	Study design	Key epidemiological findings
L Yang (6)	Jan 1998–Dec 2009	Clinical impact	Cause-specific deaths	Ecological study	127 all-cause excess deaths were associated with pH1N1. The excess mortality rates associated with pH1N1 were highest in the elderly
JT Wu (7)	Apr–Dec 2009	Clinical impact	Serum samples Blood donors: 12217 Hospital outpatients: 2520 Subjects from community: 917	Cross-sectional study	The ICU admission rate and death rate were 17.6 and 4.4 cases per 100 000 population among individuals of age 5–59 years, and older adults had higher risk of ICU admission and death, compared with school-age children
JT Wu (8)	Apr–Dec 2009	Clinical impact	Serum samples Blood donors: 12217 Hospital outpatients: 2520 Subjects from community: 917	Cross-sectional study	Young adults (20–29 years) had the lowest risk 0.39% of hospitalization if infected with pH1N1, while children aged 5–14 had the highest risk of hospital admission (0.8%)
BJ Cowling (10)	May–Nov 2009	Clinical impact	All laboratory-confirmed pH1N1 infection in Hong Kong	Ecological study	Around 20% notified pH1N1 cases were hospitalized during the mitigation phase in Hong Kong; 1.9% and 0.8% of them were admitted to ICU or died
AIX Zhang (11)	May 2009–Feb 2010	Clinical impact	Serum sample: Baseline: 795 Pandemic: 1000 Laboratory-confirmed cases: 27116	Cross-sectional study	Individuals aged 51–60 years had highest risk of developing severe diseases if infected with pH1N1, compared with younger individuals
S Riley (19)	Jul 2009–Feb 2010	Clinical impact	Paired serum samples: 770	Cohort study	Young individuals (<60 years) had about 1% risk of hospitalization if infected, while those aged >60 years had a slightly increased risk. The risk of death was highest in older people (>60 years: 220 per 100 000), but lowest in young ages (3–19 years: 1.3 per 100 000)
Q Liao (28)	Dec 2005–Mar 2006, May 2009	Comparison of psychological and behavioral response to avian A/H5N1 and pandemic A/H1N1 infection	Respondents for the avian A/H5N1 survey: 1760 Respondents for the pandemic A/H1N1 survey: 1016	Serial cross-sectional study	Knowledge on avian A(H5N1) or pH1N1 and perceived personal hygiene practices effectiveness were associated with personal hygiene practices. Improving trust in formal information would increase personal hygiene practices
JY Siu (29)	Mar–Jul, 2009	Psychological and behavioral response	Hong Kong residents with chronic renal diseases: 30	Cross-sectional study	Past experiences in the SARS outbreak greatly affected the knowledge perception and the adoption of preventive behaviors during pH1N1 among patients with chronic renal diseases
BJ Cowling (30)	Apr–Nov, 2009	Psychological and behavioral responses	Respondents: 12965	Cross-sectional study	There was a lack of changes in preventive measures and knowledge about the disease in the general population, implying a less effective role played by community mitigation measures in alleviating the impact of the pandemic

Table 2. (Continued)

First author	Study period	Scope of study	Sample/data and sample size	Study design	Key epidemiological findings
JTF Lau (31)	May 2009	Psychological and behavioral response	Respondents: 550	Cross-sectional study	The Hong Kong population demonstrated vigilance and preparedness to a potential influenza pandemic
JTF Lau (32)	May–Jun 2009	Behavioral responses	Respondents: 999	Cross-sectional study	Preventive behaviors were adopted by the public. A number of factors were associated with the maintenance of preventive behaviors
JTF Lau (33)	May–Jun 2009	Behavioral responses	Respondents: 999	Cross-sectional study	The public remained vigilant with frequent adoption of preventive measures and was generally supportive of the government although commonly with misconceptions regarding the disease
JTF Lau (34)	May–Jun 2009	Behavioral responses	Respondents: 999	Cross-sectional study	During the pre-community spread phase of the influenza pandemic, a high prevalence of avoidance behaviors among the population was identified, and cognition was found to be associated with avoidance behaviors and emotional distress
EMY Wong (35)	May–Jun 2009	Psychological and behavioral response to the outbreak and preventive measures	Respondents: 1169 teachers	Cross-sectional study	School teachers in Hong Kong were aware of and worried about pH1N1 at the early phase of the epidemic
SM Griffiths (36)	Jun 2009	Psychological and behavioral response to preventive measures	Respondents: 359 summer school students	Cross-sectional study	Largely positive responses to pH1N1 control measures were observed in the university among the students, but varied in groups by country of study
Q Liao (37)	Jun 2009	Protective behaviors	Respondents: 1001	Cross-sectional study	Trust in government/media information was associated with greater self-efficacy of infection prevention and more hand washing, while trust in informal information was related to perceived health threat and avoidance behaviors
ELY Wong (38)	Jun 2009	Psychological responses among healthcare workers	Healthcare workers: 10	Cross-sectional study	A variety of concerns existed in the frontline healthcare professionals during the pandemic
ELY Wong (39)	Jun 2009	Psychological and behavioral responses in healthcare workers	Community nurse respondents: 401	Cross-sectional study	Less than one-quarter of community nurses would be willing to provide care to patients during the influenza pandemic
SYS Wong (40)	Jun–Jul 2009	Psychological and behavioral responses	Respondents: 267	Cross-sectional study	Acceptability of pandemic influenza vaccination was low among community nurses during the period with pandemic alert level of 6
JTF Lau (41)	Jul 2009	Psychological and behavioral response	Respondents: 301	Cross-sectional study	The acceptability of pandemic influenza vaccine was low during the pandemic alert phase 6, and sensitive to personal cost
JTF Lau (42)	Jul 2009	Psychological and behavioral response	Respondents: 301	Cross-sectional study	Previous seasonal influenza vaccination, perceived side effects of the vaccine, and the experience from the family and friends might be the predictor of pandemic influenza vaccine uptake

Table 2. (Continued)

First author	Study period	Scope of study	Sample/data and sample size	Study design	Key epidemiological findings
JY Siu (43)	Dec 2009–Mar 2010	Psychological response	Respondents: 40 chronic renal disease patients	Cross-sectional study	There were misperceptions among patients with chronic renal diseases regarding pH1N1 vaccination. Inaccessibility and financial cost might also prevent the patients from receiving the vaccine
Q Liao (44)	Jan–Mar 2010	Psychological and behavioral responses	Respondents: 1443 Respondents at follow-up: 896	Serial cross-sectional study	Perceived low risk of pH1N1 infection and perceived high risk from pH1N1 vaccine inhibited the uptake of the vaccine. Vaccination intention is not a reliable predictor for future vaccine uptake
JSY Chor (45)	Jan–Mar 2009, May 2009	Psychological and behavioral response	Healthcare workers in the 1st survey: 1866 Healthcare workers in the 2nd survey: 389	Serial cross-sectional study	Generally low acceptability of pre-pandemic influenza vaccine was observed, and no significant changes were detected through the transition of the WHO alert level from phase 3 to 5
JSY Chor (46)	Jan–Apr 2010	Psychological and behavioral response	Healthcare worker respondents: 2100	Cross-sectional study	The acceptance of pandemic influenza vaccine was generally low among healthcare workers, and seasonal vaccination experience could be the predictor of the pandemic influenza vaccine uptake
KK Mak (47)	May 2009	Psychological and behavioral response	Secondary school students: 288	Cross-sectional study	Hong Kong secondary school students showed poor knowledge of the 2009 influenza A(H1N1) pandemic, low perceived risk. The adoption of preventive precautions was not prevalent and associated with female sex, better knowledge, and higher perceived risk
GC Mak (48)	Jan 2004–Jul 2011	Ecologic impact	Respiratory illness surveillance data	Ecological study	Changes in the dynamics of other circulating respiratory viruses after the 2009 pandemic were possibly induced by virus interference

Table 3. Summary of studies on the control of 2009 pandemic influenza A(H1N1) in Hong Kong

First author	Study period	Scope of study	Sample/data and sample size	Study design	Key epidemiological findings
IW Li (50)	Apr–Jun 2009	Effect of oseltamivir	Cases without treatment: 27 Cases treated by oseltamivir: 118	Case–control study	Oseltamivir can suppress viral load more effectively when given early in mild cases of pH1N1 infection
YH Leung (51)	May–Jun 2009	Effect of oseltamivir	Laboratory-confirmed patients: 56 Respiratory specimen collected: 341	Observational study	Patients infected with pH1N1 who received oseltamivir >48 hour after illness onset had a longer duration of viral shedding, compared with those started treatment within 48 hour
YH Leung (13)	Jun 2009	Effect of oseltamivir	Exposed students: 511 Infected students: 65	Observational study	Oseltamivir prophylaxis might protect contacts of confirmed cases against confirmed infection
JHS You (52)	2010–2011	Cost-effectiveness of oseltamivir	Household contacts: 205 Hospitalized patients with suspected influenza	Ecological study	Empirical antiviral treatment appeared to be a cost-effective strategy during influenza epidemics in managing hospitalized patients with severe respiratory infection suspected of influenza
BJ Cowling (53)	Nov 2008–Oct 2009	Efficacy of vaccine	Vaccinated households: 71 Placebo control household: 48	Randomized controlled trial	Trivalent seasonal influenza vaccine protected strain-matched infection in children, and previous seasonal influenza infection might confer cross-protection against pandemic influenza
TC Chan (54)	Dec 2009–Dec 2010	Efficacy of vaccine	Institutionalized elderly: 711	Cohort study	Dual vaccination with both pandemic and seasonal influenza vaccines reduced all-cause mortality and hospitalization
M Tarrant (49)	Feb–Jun 2010	Effectiveness of vaccination strategy	Postpartum women: 549	Cross-sectional study	The uptake of the pH1N1 vaccine among Hong Kong pregnant women was unacceptably low. Interventions to increase knowledge of influenza vaccine and uptake among this group should be a priority for future pandemic planning
HK Wong (55)	Sep 2009	Feasibility of a immunotherapy program	Contacted recovered patients: 9101 Subjects eligible for plasma donation: 493 Plasma donors: 301	Observational study	Collecting convalescent plasma from recovered patients to produce hyperimmune intravenous globulin was feasible, but faced difficulties and obstacles in practice
IFN Hung (56)	Sep 2009–Jun 2011	Effectiveness of immunotherapy	Patients in the treatment group: 20 Patients in the control group: 73	Case–control study	In the clinical setting, treating severe pH1N1 infections with convalescent plasma could reduce respiratory tract viral load, serum cytokine response, and mortality of the patients

Table 3. (Continued)

First author	Study period	Scope of study	Sample/data and sample size	Study design	Key epidemiological findings
JT Wu (57)		Feasibility and benefits of an immunotherapy program	NA	Operational study	Passive immunotherapy with convalescent blood products collected from donors recovered from previous pandemic influenza infection is a logistically feasible mitigation option
VCC Cheng (58)	May–Aug 2009	Control of nosocomial transmission with mask wearing	Laboratory-confirmed Inpatients/contacts: 311/331 healthcare workers/contacts: 12/370 All laboratory-confirmed pH1N1 infection in Hong Kong	Observational study	Wearing masks could prevent nosocomial pH1N1 infection
JT Wu (9)	May–Aug 2009	Control of transmission with school closure		Ecological study	School closure could reduce pH1N1 transmission among children by 70%, and 25% of transmission overall
BJ Cowling (59)	Jul–Aug 2009	Effectiveness of entry screening	35 countries with >100 confirmed H1N1 cases by Jul 6, 2009	Cross-sectional study	Entry screening may lead to short-term delays in local transmission of pH1N1
KKC Chan (60)	May 2009–Feb 2010	Effectiveness of extracorporeal membrane oxygenation for treating acute respiratory distress syndrome in pH1N1	Severe pH1N1 patients: 120	Observational study	Treating severe pH1N1 infections with acute respiratory distress syndrome by extracorporeal membrane oxygenation in Hong Kong demonstrated similar effectiveness as previous studies

influenza vaccination history, and fear of side effects.^{46,49} Given the essential role of healthcare workers in fighting against the pandemic, their responses to the pandemic were also investigated. Around one-quarter of community nurses reported being unwilling to take care of patients during the pandemic.³⁹ However, during the pandemic period, healthcare workers who worked in isolation wards showed a general willingness and strong sense of duty to work.³⁸

Control of pH1N1

Information on the effectiveness and impact of control measures on pH1N1 was reported in 14 studies^{9,13,49–60} (Table 3). In terms of public health measures, one study estimated that the entry screening measures adopted by Hong Kong and other countries could not have delayed local transmission substantially.⁵⁹ Closure of kindergartens and primary schools from mid-June to July 2009 was estimated to reduce transmission within children by 75%.⁹

Treatment of pH1N1 patients with oseltamivir was demonstrated to be effective in suppressing viral load and shortening duration of viral shedding when administered within 48 hours of illness onset,^{50,51} and empirical treatment was found to be a cost-effective strategy for managing patients hospitalized with severe respiratory infection suspected of influenza.⁵² Treatment of severe pH1N1 infections with hyperimmune intravenous globulin produced from convalescent plasma collected from recovered patients was able to the risk of death by 80% and to improve the profile of viral shedding and cytokines in a small number of patients with severe illness.⁵⁶ The logistical feasibility of passive immunotherapy was demonstrated in scenarios with relatively lower donor percentage (5–15%) and limited capacity of blood screening and processing.⁵⁷

No studies reported efficacy or effectiveness of the monovalent pH1N1 vaccine in Hong Kong. One study investigated the efficacy of seasonal trivalent inactivated vaccine and found some evidence that vaccinated children might face a higher risk of pH1N1, although the biological mechanism was unclear.⁵³ In a cohort of institutionalized elderly followed through 2010, dual vaccination with the monovalent pH1N1 and trivalent seasonal vaccines was estimated to reduce all-cause mortality by 54% and 74% compared with seasonal vaccine alone and no vaccine,⁵⁴ although surveillance data indicated that pH1N1 was not prevalent during this period. In a hospital setting, not wearing a mask was a possible risk factor for nosocomial transmission.⁵⁸

Discussion

The epidemiological and public health research response to pH1N1 in Hong Kong covered many essential areas of research into pH1N1 epidemiology (Table 4). In particular, integration of different expertise from various angles of

Table 4. Important research findings and public health implications contributing to knowledge about pH1N1

Key Components of epidemiologic investigations (69)	Corresponding research response in Hong Kong	References
Defining cases	Frequency of each clinical symptom was examined in household contacts	(18)
Establishing cumulative incidence of infection	Seroepidemiological studies permitted straightforward estimation of the age-specific cumulative incidence of infection	(7,8)
Descriptive epidemiology with respect to time, space, and person	The effective reproduction number was around 1.4–1.5 at the start of the epidemic	(10)
	The probability of confirmed infection among household contacts was around 9% and similar to seasonal influenza, while children had a higher risk of being infected compared with adults	(12,18)
	Geographic clustering of confirmed cases was identified	(15)
	Psychological responses among the general population were assessed	(28–46)
	The age-specific risk of severe illness and death was estimated on a per-infection basis	(7,8)
Identification of risk factors	Healthcare workers were not at particularly high risk of infection	(17,22)
	Underlying comorbidities of severe cases with pH1N1 were different from those for seasonal influenza	(24,70)
Pharmaceutical interventions	Timely antiviral therapy (<48 hours of symptom onset) with oseltamivir could reduce viral load, duration of viral shedding among patients, and protect contacts against infection	(13,50,51)
	Intention to receive the pandemic vaccine was low in the general population and healthcare workers	(40–42,44–46)
	Passive immunotherapy might reduce the risk of mortality by around 80% in severe pH1N1 infections	(56)
Non-pharmaceutical interventions	School closures can reduce intra-age-group transmission among children by 70% and overall transmission by 25%	(9)
	Entry screening did not yield substantial delay in the spread of pH1N1	(59)
	Mask wearing might prevent nosocomial infection among healthcare workers	(58)

approaches to influenza has allowed Hong Kong researchers to study specific epidemiological aspects with a range of modern approaches including detailed household transmission studies, real-time seroepidemiological surveys, and mathematical modeling. Estimates of transmissibility and severity of pH1N1 in Hong Kong were consistent with observations in other countries.^{61–63} However, the clinical impact was moderate, as most infections were associated with mild disease. Only 63 local deaths were associated with confirmed pH1N1 infection during the first wave between April and December 2009, and 127 excess deaths⁶ compared with around 1000 excess deaths associated with seasonal influenza every year in Hong Kong.⁶⁴ The general public, perhaps sensitized by previous experiences with infectious disease epidemics including SARS, showed little concern or behavioral changes once the mild severity profile of pH1N1 became clear.^{28,30,32,37} School closures were effective in suppressing transmission, although incidence rose rapidly once schools reopened in September and half of the school-age children were infected by the end of the first wave.⁸ The use of convalescent plasma to treat severe infections was shown to be feasible in a pandemic⁵⁷ and evidence of its effectiveness albeit from a small study should justify further studies.⁵⁶

While we focused on research into the epidemiology, impact, and control of pH1N1, much important research on pH1N1 has been carried out in other areas outside the scope of our review. To give two specific examples, local researchers confirmed the origins of the 2009 pandemic strain by comparison with a detailed local swine influenza surveillance program,⁶⁵ and performed important basic studies on pathogenesis.⁶⁶

Two sets of studies made particularly important contributions to international knowledge on pH1N1 epidemiology. First, household transmission studies allowed detailed inferences on the transmissibility of pH1N1 as well as the (mild) clinical profile of cases in the community.^{12,13,18} Household studies have the unique advantage of a natural setting that allows comparisons of transmission characteristics and the effects of host, viral, and environmental factors on transmission. While the highest pH1N1 infection attack rates occurred among school-age children, investigations of school outbreaks can tend to overestimate transmissibility because of selection bias where larger outbreaks are more likely to be identified and studied. Second, serologic studies allowed robust inference on the cumulative incidence of infection through the first wave of pH1N1,^{7,8,11,19,26} and when combined with surveillance data on severe cases allowed accurate

Table 5. Factors associated with the rapid and comprehensive research response to 2009 pH1N1 in Hong Kong

Key factors	Components
Improvement of public health infrastructure	Establishment of the Centre for Health Protection in 2004 to improve preparedness and response to disease outbreaks Establishment of scientific committees in the government early in the pandemic to provide guidance to policy makers
Creation of a supportive environment for academic research	Identification of the essential role of scientific evidence in guiding health policy and consequently building capacity in infectious disease research Encouragement and development of a multidisciplinary research approach through collaborative studies and regular joint meetings Establishment of a system for rapid review and funding for projects in public health emergencies Expedited IRB review and approval procedures to ensure rapid initiation of research projects during public health emergencies
Sustained development of multidisciplinary academic expertise	Maintenance of routine active research into influenza across disciplines Initiation of a rapid research response to pH1N1 based on established research facilities and resources

estimates of the severity profile of pH1N1 on a per-infection basis.^{7,8,11,19} It can be challenging to estimate the cumulative incidence of infection based on data on numbers of confirmed cases, or from routine surveillance of illnesses presenting to healthcare settings, because of the unknown proportion of infections that are subclinical and potential changes in healthcare-seeking behavior in a pandemic.⁶⁷

The rapid and comprehensive research response to pH1N1 in Hong Kong can be attributed to a number of factors, such as improvements in public health infrastructure, creation of a supportive environment for academic research, and sustained development of multidisciplinary academic expertise (Table 5).

There were some limitations of the research response. While the unique setting in Hong Kong facilitated some of the studies discussed here, the uniqueness was also a limitation when considering the generalization of research findings. Given the importance of children in the spread of influenza, greater attention could have been given to outbreak dynamics in schools and in particular the many outbreaks in September 2009 once schools reopened after summer vacation. Oseltamivir was widely prescribed to confirmed cases including those with mild disease, yet there has been no systematic evaluation of the effectiveness or cost-effectiveness of this policy. Finally, there has not yet been a thorough investigation of the dynamics of the second wave of pH1N1 in January–February 2011, which unexpectedly had a similar clinical impact to the first wave. Considering future infectious disease epidemics, Hong Kong may be one of the few settings where we have the opportunity to conduct a more concerted and consolidated investigation of the epidemic at an individual level. For instance, we believe that Hong Kong is equipped with the infrastructure to plan a multidisciplinary

(i.e., clinical, epidemiological, and virological) program of investigation of early cases such as the first few hundred (FF100) study in the United Kingdom in 2009.⁶⁸

There are some limitations of our review. First, our review only included studies published within around 3 years of the start of the pandemic, and some studies may not have been published yet or may even be ongoing. While the pH1N1 virus was not prevalent through 2010, a second wave of infection occurred in January and February 2011 with a similar clinical impact to the first wave, although detailed epidemiologic examinations of the second wave have not yet been reported. Second, Hong Kong is a densely populated city with a developed economy, and some epidemiologic findings may not generalize to other settings. For example, transmission dynamics may vary owing to the high population density or the subtropical environment, mortality among hospitalized patients may be lower than in other settings with less investment in healthcare facilities, while the population impact may differ owing to the unique historical experiences of the local population with infectious diseases. Nevertheless, many aspects of pH1N1 epidemiology appear to have been similar in Hong Kong to other developed settings.

In conclusion, there was a rapid and comprehensive research response to pH1N1 in Hong Kong, providing important information on the epidemiology, impact, and control of the novel virus with relevance internationally as well as locally. The scientific knowledge gained through detailed studies of pH1N1 is now being used to revise and update pandemic plans and preparedness. The experiences of the research response in Hong Kong may also provide a template for the research response to future emerging and reemerging disease epidemics.

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Conflicts of interest

BJC has received study funding from MedImmune Inc and consults for Crucell MV. DKMI has received study funding from F. Hoffmann-La Roche. The authors report no other potential conflicts of interest. We declare that we have each participated in the conception, design, analysis, and writing of the report and that we have read and approved the final version.

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