Original Contribution

Estimates of the Transmissibility of the 1968 (Hong Kong) Influenza Pandemic: Evidence of Increased Transmissibility Between Successive Waves

Charlotte Jackson*, Emilia Vynnycky, and Punam Mangtani

* Correspondence to Charlotte Jackson, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom (e-mail: charlotte.jackson@lshtm.ac.uk).

The transmissibility of the strain of influenza virus which caused the 1968 influenza pandemic is poorly understood. Increases in outbreak size between the first and second waves suggest that it may even have increased between successive waves. The authors estimated basic and effective reproduction numbers for both waves of the 1968 influenza pandemic. Epidemic curves and overall attack rates for the 1968 pandemic, based on clinical and serologic data, were retrieved from published literature. The basic and effective reproduction numbers were estimated from 46 and 17 data sets for the first and second waves, respectively, based on the growth rate and/or final size of the epidemic. Estimates of the basic reproduction number (R_0) were in the range of 1.06–2.06 for the first wave and, assuming cross-protection, 1.21–3.58 in the second. Within each wave, there was little geographic variation in transmissibility. In the 10 settings for which data were available for both waves, R_0 was estimated to be higher during the second wave than during the first. This might partly explain the larger outbreaks in the second wave as compared with the first. This potential for change in viral behavior may have consequences for future pandemic mitigation strategies.

basic reproduction number; disease outbreaks; influenza, human; models, theoretical; Orthomyxoviridae

The current pandemic of novel H1N1 influenza illustrates the ability of novel influenza viruses to spread rapidly through populations. H1N1 first emerged in spring 2009, and a second wave is expected in the Northern Hemisphere in the autumn. The 1968 (Hong Kong) H3N2 influenza pandemic also occurred in 2 waves, the second being more severe than the first in many settings (1–9). Like H1N1 (and H5N1, another influenza virus with pandemic potential), the H3N2 virus was not completely antigenically novel but shared its neuraminidase with the H2N2 virus, which had circulated for the preceding 10 years.

The impact of any pandemic depends to a great extent on the transmissibility of the causal pathogen, which is usually described using the basic reproduction number, R_0 (the average number of secondary infectious cases resulting from an infectious person's introduction into a totally susceptible population). The equivalent statistic in a partially susceptible population is the effective (net) reproduction number, R_n. According to several studies, the R_0 of the 1918 H1N1 (10–16) and 1957 H2N2 (12, 13, 17) pandemic influenza viruses was between 1.2 and 3. The characteristics of the H3N2 pandemic influenza virus are poorly understood. Estimates of its reproduction numbers have primarily been based upon data from the second wave (11–13, 18); in a study based on national general practice consultation data from England and Wales, Hall et al. (19) estimated that R_n increased slightly between successive waves, from 1.28 to 1.56. Several estimates have been based upon mortality data (11, 13, 18), and all but 2 (20, 21) were based on national (11, 13, 18, 19) or city-level (12, 18) data from England and Wales. Few studies have explored temporal or geographic variation in the R_0 of the 1968 pandemic virus.

In this study, we reviewed morbidity and serologic data from diverse settings for the first and second waves of the 1968 influenza pandemic to determine the extent to which R_0 and R_n differed temporally, geographically, and between successive waves.

Table 1.   Data Sets From Open Settings Used in Analyses of the H3N2 Influenza Pandemic of 1968

Setting	Wave	Observation Period[a]	Case Definition/ Source of Data	% of Population Meeting Case Definition[b]	No. of Persons Meeting Case Definition	Size of Eligible Population	% of Population Susceptible to Infection at Beginning of Wave	Method Used to Estimate R_0	Length of Period Used to Estimate Growth Rate, weeks
Hong Kong (36)	1	May 27, 1968–September 28, 1968	Cases of ILI reported weekly to the Epidemiological Office from 6 outpatient departments and hospitals	N/A			100[c]	Growth rate	4
Bangkok/ Dhonburi, Thailand (37)	1	July 29, 1968–December 1, 1968	Attendance at an outpatient clinic of Siriraj Hospital with clinical diagnosis of influenza	N/A			100[c]	Growth rate	6
		July 29, 1968–November 17, 1968	Physician's diagnosis of influenza reported in a questionnaire survey of school students and their families and medical students	N/A			100[c]	Growth rate	9
Panama Canal Zone (22)	1	August 5, 1968–November 10, 1968	Clinic visits for acute respiratory infection in Paraíso and Pedro Miguel, Panama, for patients aged ≥3 years	N/A			94[d]	Growth rate	4
		November 1968	≥4-fold increase in HI antibody titer since June/July 1968 in serologic survey of laboratory workers	26	15	57	93[e]	Final size	
		September 1, 1968–October 31, 1968	Clinical ILI reported in a retrospective survey of families in Paraiso and Pedro Miguel	46	235	516	94[d]	Final size	
Kansas City, Missouri, United States (23)	1	November 4, 1968–January 18, 1969	Self-reported ILI (defined as "an illness with the symptoms of fever, cough, muscle aches and pains, headache, and sore throat") in a retrospective questionnaire survey of high school students and their families	39	2,711	6,994	100[c]	Growth rate, final size	7
		November 4, 1968–January 18, 1969	HI antibody titer ≥1:10 in a serologic survey of a subgroup of students	49	139	285	100[c]	Final size	
		November 4, 1968–January 18, 1969	HI antibody titer ≥1:10 and self-reported ILI (defined as above) in the same subgroup of students	28	81	285	100[c]	Growth rate	5

Location (ref)	Wave	Period	Data	N/A col			Estimate	Method	R
Philadelphia, Pennsylvania, United States (35)	1	October 29, 1968–December 22, 1968	Weekly laboratory-confirmed Hong Kong influenza isolates	N/A			100[c]	Growth rate	4
United Kingdom (2)	1	December 23, 1968–June 22, 1969	Influenza and ILI reported to the General Practice Research Unit of the RCGP, for patients consulting 40 general practices	N/A			90 (based on ref. 24)	Growth rate	8
		Summer 1969	HI antibody titer ≥1:10 in serologic survey of serum samples from adults sent to the PHLS for other tests	57	631	1,104	58[d]	Final size	
		November 4, 1968–April 6, 1969	Weekly laboratory-confirmed influenza cases (influenza A virus isolations and cases with ≥4-fold increase in antibody titer) reported to the PHLS by hospital and public health laboratories	N/A			90 (based on ref. 24)	Growth rate	6
United Kingdom (7)	1	December 9, 1968–April 20, 1969	Clinical influenza cases reported by the RCGP	N/A			90 (based on ref. 24)	Growth rate	9
United Kingdom (2)	2	November 3, 1969–April 5, 1970	Influenza and ILI reported to the General Practice Research Unit of the RCGP, for patients consulting 40 general practices	N/A			65 (based on ref. 24)	Growth rate	8
		Summer 1970	HI antibody titer ≥1:10 in serologic survey of serum samples from adults sent to the PHLS for other tests	70	1,502	2,139	43[d]	Final size	
		November 10, 1969–February 22, 1970	Weekly laboratory-confirmed influenza cases (influenza A virus isolations and cases with ≥4-fold increase in antibody titer) reported to the PHLS by hospital and public health laboratories	N/A			65 (based on ref. 24)	Growth rate	5
United Kingdom (7)	2	December 8, 1969–April 5, 1970	Reports to the PHLS of influenza A virus isolations and cases with a ≥4-fold increase in antibody titer from public health and hospital laboratories	N/A			65 (based on ref. 24)	Growth rate	6

Table continues

Table 1. Continued

Setting	Wave	Observation Period[a]	Case Definition/ Source of Data	% of Population Meeting Case Definition[b]	No. of Persons Meeting Case Definition	Size of Eligible Population	% of Population Susceptible to Infection at Beginning of Wave	Method Used to Estimate R_0	Length of Period Used to Estimate Growth Rate, weeks
Scotland (8)	1	December 30, 1968–June 15, 1969	Returns from laboratories of viral isolations, ≥4-fold increase in antibody titer, or high single antibody titer	N/A			90 (based on ref. 24)	Growth rate	7
	2	December 1, 1969–April 26, 1970	Returns from laboratories of viral isolations, ≥4-fold increase in antibody titer, or high single antibody titer				65 (based on ref. 24)	Growth rate	8
Cirencester, United Kingdom (38)	1	November 27, 1968–April 15, 1969	Weekly GP consultations for febrile respiratory disease	N/A			90 (based on ref. 24)	Growth rate	10
Sheffield, United Kingdom (24)	1	May–July 1969	HI antibody titer ≥1:6 in serologic survey of blood donors, antenatal clinic attendees, and samples submitted for other tests	35	160	454	90[d]	Final size	
Lambeth, London, United Kingdom (2)	1	Summer 1969	≥4-fold increase in HI antibody titer in serologic survey of men living in the London borough of Lambeth	31	112	367	81[d]	Final size	
	2	Summer 1970	≥4-fold increase in HI antibody titer in serologic survey of men living in the London borough of Lambeth	28	85	302	52[d]	Final size	
West Nile District, Uganda (25)	1	November 1969	HI antibody titer ≥1:20 in serologic survey of samples collected during an unrelated survey	17	19	115	100[c]	Final size	
Kabale, Uganda (25)	1	January 1970	HI antibody titer ≥1:20 in serologic survey of randomly selected outpatients and staff at Kabale Hospital	22	16	73	100[c]	Final size	
Czechoslovakia (39)	1	January 6, 1969–June 1, 1969	Weekly reported clinical influenza cases in Czechoslovakia, Czech Socialist Republic, and 5 districts individually	N/A			100[c]	Growth rate	4–8, depending on district

Location (ref.)	Wave	Period	Description				%	Method	
Moscow, Union of Soviet Socialist Republics (32)	1	January–February 1969	"Morbidity" in adult placebo group in trial of prophylactic interferon	18	551	3,129	100[c]	Final size	
			"Morbidity" in older children's (ages 7–12 years) placebo group in trial of prophylactic interferon	20	413	2,055	100[c]	Final size	
Donetsk, Ukraine (32)	1	Not stated	"Morbidity" in young children's (ages 2–6 years) placebo group in trial of prophylactic interferon	12	53	454	100[c]	Final size	
São Paulo, Brazil (4)	1	February 1969	HI antibody titer ≥1:10 in serologic survey	70	684	980	73[d]	Final size	
	2	1970	HI antibody titer ≥1:10 in serologic survey	74	588	790	30[d]	Final size	
Khartoum, Sudan (9, 27)	2	After May 1970	Complement-fixing antibody titer ≥1:10 in serologic survey of outpatients and serum samples submitted for other tests in Khartoum, Omdurman, and Khartoum North	64	123	192	50[c]	Final size	
		November 3, 1969–May 30, 1970	Cases of ILI reported weekly to outpatient departments in hospitals and health centers in Khartoum	N/A			50[c]	Growth rate	5
Sydney, New South Wales, Australia (5)	1	May 1970	"Demonstrable antibodies" in serologic survey of blood donors	40	213	538	94[d]	Final size	
	2	September 1970	≥4-fold increase in HI antibody titer since May 1970 in serologic survey of blood donors	21	159	760	60[d]	Final size	
Epping, New South Wales, Australia (6)	1	Approximately July–August 1969	Cases of ILI reported during retrospective surveys of GP patients and their families who consulted a GP for any reason after the epidemic (excluding vaccinees)	16	176	1,099	94 (based on ref. 5)	Final size	
	2	Approximately June–August 1970	Cases of ILI reported during retrospective surveys of GP patients and their families who consulted a GP for any reason after the epidemic (excluding vaccinees)	24	305	1,275	60 (based on ref. 5)	Final size	

Table continues

Table 1.   Continued

Setting	Wave	Observation Period[a]	Case Definition/ Source of Data	% of Population Meeting Case Definition[b]	No. of Persons Meeting Case Definition	Size of Eligible Population	% of Population Susceptible to Infection at Beginning of Wave	Method Used to Estimate R_0	Length of Period Used to Estimate Growth Rate, weeks
Epping, New South Wales, Australia (33)	1	Approximately July–August 1969	Cases of ILI reported during retrospective surveys of GP patients and their families who consulted a GP for any reason after the epidemic (excluding vaccinees)	19	150	808	94 (based on ref. 5)	Final size	
New South Wales, Australia (6)	1	June 21, 1969– September 12, 1969	Weekly Hong Kong influenza virus isolates at Institute of Clinical Pathology and Medical Research	N/A			94 (based on ref. 5)	Growth rate	4
Guatemala (40)	2	August 10, 1969– December 27, 1969	Weekly reported cases of ILI	N/A			50[c]	Growth rate	7
Doncaster, United Kingdom (1)	2	November 26, 1969–January 20, 1970	Weekly GP consultations for clinical influenza	N/A			65 (based on ref. 24)	Growth rate	4
		November 26, 1969–January 20, 1970	"Probable influenza" as judged by response to questionnaire survey of random sample of patients registered with a general practice	20	108	530	65 (based on ref. 24)	Final size	
Mombasa, Kenya (26)	2	February 1970	HI antibody titer ≥1:20[f] in serologic survey of randomly selected patients receiving treatment at a hospital	37	21	57	100[c,g]	Final size	
Arusha, Tanzania (26)	2	February 1970	HI antibody titer ≥1:20[f] in serologic survey of randomly selected patients receiving treatment at a hospital	72	65	90	100[c]	Final size	

Abbreviations: GP, general practitioner; HI, hemagglutination-inhibiting; ILI, influenza-like illness; N/A, not applicable; PHLS, Public Health Laboratory Service; RCGP, Royal College of General Practitioners.

[a] Period covered by incidence data or time at which serum samples were taken.

[b] For data sets with good ascertainment only. For serologic data, the proportion of the population meeting the case definition is not necessarily equivalent to the proportion experiencing infection during the given wave (as seropositivity may reflect infection either during that wave or previously). "N/A" means that ascertainment was incomplete. Numerators may include persons who did not report the date of onset of illness and therefore were not included in estimation of R_0 using the epidemic growth rate.

[c] Assumed proportion susceptible.

[d] Proportion susceptible based on the original data set or on data cited in the original paper.

[e] Data cited in the paper implied that 94% of persons in the wider population were likely to be susceptible; however, because of the small size of this sample, it was necessary to round to 93%.

[f] Case definition not given, but comparison with reference 25 suggests this definition.

[g] Although these data refer to the second wave, the data were inconsistent with 50% of individuals being susceptible at the start of the wave. Therefore, it was assumed that all persons were initially susceptible.

MATERIALS AND METHODS

Data sources

We searched PubMed and CAB Direct from 1966 to 2006 for English-language studies that presented data on 1) the proportions of persons who experienced infection (as implied by serologic analysis) or clinical disease and 2) weekly numbers of cases during the first and/or second waves of the 1968 influenza pandemic. Reference lists in the articles retrieved were also searched, and key journals (including *Bulletin of the World Health Organization*, *British Medical Journal*, and *Weekly Epidemiological Record*) from 1968–1970 were hand-searched. Age-stratified data were also obtained where possible. The data sets (Tables 1 and 2) were classified as referring to either confined (e.g., military bases, ships, homes, schools) or open (cities or national populations) settings. Data sets which clearly included vaccinated persons were excluded. The first and second waves were defined from the identified reports, based on the timing of the global circulation of the virus: approximately July 1968 to August 1969 for the first wave and September 1969 to September 1970 for the second.

Serologic data. We identified 25 suitable serologic data sets (17 for the first wave, 8 for the second (2–5, 22–31)). The definition of infection varied (Tables 1 and 2) but was frequently either a hemagglutination-inhibiting antibody titer of $\geq$1:10 or a $\geq$4-fold increase in hemagglutination-inhibiting antibody titer. For consistency, when hemagglutination-inhibiting antibody titers were presented without a definition of infection, a titer of $\geq$1:10 was taken as positive.

Clinical attack rates. We identified 11 data sets (9 for the first wave, 2 for the second (1, 6, 22, 23, 32–35)) with suitable data on the proportion of persons who experienced clinical disease (i.e., clinical attack rates). These were data sets in which ascertainment appeared to be good—for example, from retrospective surveys or intervention studies. Case definitions were taken from the original data sets. We calculated 95% exact binomial confidence intervals for both the clinical attack rates and the proportions seropositive.

Epidemic curves. We identified 27 suitable data sets (20 for the first wave, 7 for the second (1, 2, 6–9, 22, 23, 35–40)) on the weekly number of clinical cases (see Web Figure 1, which is posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/)). Data sets involving small numbers of cases (e.g., <25) or irregular increases in case numbers were excluded.

Analyses of attack rates and reproduction numbers

Calculation of susceptible attack rates. For settings in which the proportion of persons seropositive before and after one or both waves was available, the susceptible attack rate (AR$_{sus}$) was calculated as

$$\text{AR}_{\text{sus}} = \frac{P_{\text{post}} - P_{\text{pre}}}{1 - P_{\text{pre}}},$$

where P_{pre} and P_{post} are the proportions seropositive before and after the given wave, respectively. We estimated 95%

credible intervals for the susceptible attack rate by Monte Carlo sampling of posterior distributions of the proportion seropositive in each wave, using conjugate properties of the beta distribution with binomial priors (41). Here, P_{pre} and P_{post} were treated as though they were independent.

Estimation of R_0. R_0 was estimated for each data set using either the final size of the epidemic (for serologic data and clinical data with good ascertainment) or its growth rate (for epidemic curves) (42, 43) (Tables 1 and 2). These methods do not account for contact patterns in the population. Although recent studies have suggested that contact patterns are age-dependent (44), the attack rates in the age-stratified data we retrieved did not vary with age (Web Figures 2 and 3 (http://aje.oxfordjournals.org/)). This is paradoxical and may reflect age-related differences in susceptibility or case ascertainment. Such effects are difficult to study using the limited age-stratified data available; therefore, we restricted our analyses to data which were not age-stratified.

Estimates of R_0 using the final size of the epidemic. R_0 was estimated for the corresponding data sets (1–6, 22–35) using the equation (42)

$$R_0 = \frac{N-1}{C} \sum_{i=S_f+1}^{S_0} \frac{1}{i}, \tag{1}$$

where N is the population size, C is the number of infected persons or clinical cases (depending on the data set) recorded during the wave, and S_0 and S_f are the numbers of persons considered to be susceptible in the population at the beginning and end of the wave, respectively.

The standard error (SE) of R_0 was calculated as (42)

$$\text{SE}(R_0) = \frac{N-1}{C} \sqrt{\sum_{i=S_f+1}^{S_0} 1/i^2 + \frac{CR_0^2}{(N-1)^2}}. \tag{2}$$

R_n was estimated as $R_n = R_0 s$, where s is the proportion of the population that is susceptible to infection at the beginning of the wave. We calculated 95% confidence intervals for R_n by multiplying the respective limits on R_0 by the proportion susceptible.

Estimates of R_0 using the growth rate of the epidemic. For each epidemic curve (1, 2, 6–9, 22, 23, 35–40; Web Figure 1), R_n was estimated using the equation (43)

$$R_n = \Lambda^2 LD + \Lambda(L + D) + 1, \tag{3}$$

where L and D are the durations of the latent and infectious periods, respectively, and Λ is the growth rate in the cumulative number of cases reported during the exponential growth phase of the epidemic (calculated as the gradient of the straight line fitted to the natural logarithm of the cumulative number of cases during this phase). We estimated the length of this phase for each data set (Tables 1 and 2) by visually inspecting the plot of the natural logarithm of the cumulative number of cases against time. The latent and infectious periods were each assumed to last 2 days,

Table 2. Data Sets From Confined Settings Used in Analyses of the H3N2 Influenza Pandemic of 1968

Setting	Wave	Observation Period[a]	Case Definition/ Source of Data	% of Population Meeting Case Definition[b]	No. of Persons Meeting Case Definition	Size of Eligible Population	% of Population Susceptible to Infection at Beginning of Wave	Method Used to Estimate R_0
USS Finch, Hong Kong (28)	1	August 2, 1968– August 26, 1968	≥4-fold increase in HI and/or complement-fixing antibody titer among men providing 3 serum samples during an outbreak aboard a US naval vessel after arrival in Hong Kong	48	47	97	100[c]	Final size
Medical conference, Teheran, Iran (34)	1	September 7, 1968– September 15, 1968	Reported general and local symptoms with or without fever reported through a questionnaire survey of attendees following an outbreak at a medical conference	35	296	844	99[d]	Final size
Japanese Self-Defense Forces camps (29)	1	April 1969	≥4-fold increase in HI antibody titer since October 1968 in a serologic survey of randomly selected persons in Japanese Self-Defense Forces camps	37	495	1,325	100[c]	Final size
Japanese primary school (29)	1	November 1968	Hong Kong antibody titer ≥1:128 in a serologic survey of children in an "epidemic" primary school class	69	33	48	100[c]	Final size
Fuchu sanatorium, Japan (29)	1	April 1969	≥4-fold increase in antibody titer since February 1969 or single titer ≥1:128 in a serologic survey of patients	19	22	114	100[c]	Final size
Nakano sanatorium, Japan (29)	1	May 1969	≥4-fold increase in antibody titer since February 1969 or single titer ≥1:128 in a serologic survey of patients and staff	34	202	593	100[c]	Final size
Japanese Ground Self-Defense Forces (30)	1	May 1969	≥4-fold increase in HI antibody titer since October 1968 in a control group living in different barracks than the vaccinated group in a clinical trial of Hong Kong influenza vaccine among soldiers	63	57	90	100[c]	Final size
Elderly care home, Philadelphia, Pennsylvania, United States (35)	1	November 1968	ILI in residents during an outbreak of Hong Kong influenza	31	255	824	100[c]	Final size
Children's home, North Carolina, United States (31)	1	December 1968	Admission to infirmary with ≥4-fold increase in complement-fixing or HI antibody titer, or other serologic evidence of infection	15[d]	41	277	100[c,d]	Final size

								Final size
Royal Air Force bases, England (3)	1	Spring 1969	≥4-fold increase in HI antibody titer since autumn 1968	23	176	775		100[c]
	2	Summer 1970	≥4-fold increase in HI antibody titer since spring 1969	42	199	479		77[e]

Abbreviations: HI, hemagglutination-inhibiting; ILI, influenza-like illness.
[a] Period covered by incidence data or time at which serum samples were taken.
[b] For data sets with good ascertainment only. For serologic data, the proportion of the population meeting the case definition is not necessarily equivalent to the proportion experiencing infection during the given wave (as seropositivity may reflect infection either during that wave or previously).
[c] Assumed proportion susceptible.
[d] Excludes 3 symptomatic children from whom serum specimens were not collected.
[e] Proportion susceptible based on the original data set.

consistent with experimental data (see references in the article by Vynnycky et al. (15)). R_0 was estimated using the equation $R_0 = R_n/s$. We calculated 95% confidence intervals for R_n (and hence R_0) from the 95% confidence limits on Λ.

Equation 3 assumes that the latent and infectious periods follow the exponential distribution; however, in previous analyses of several H1N1 pandemic influenza data sets, investigators found that R_0's in most cases were very similar, irrespective of whether an exponential or tight distribution of the latent and infectious periods was assumed (15). We also used the expression $e^{\Lambda T_g}$ (where T_g is the generation time), which provides an upper bound for R_n (45), to assess whether we had underestimated R_n.

All persons in a given setting were assumed to be susceptible to infection before the first pandemic wave, unless there was evidence to the contrary (e.g., data on pre-epidemic seropositivity) from the same setting or a similar setting (Tables 1 and 2). The proportion susceptible at the start of the second wave was also based on serologic data (see Tables 1 and 2). For Guatemala and Khartoum, Sudan, serologic data were unavailable, and 50% of persons were assumed to be susceptible at the start of the second wave, which is plausible given the proportion of persons who were seropositive after the first wave elsewhere (Web Figure 4 (http://aje.oxfordjournals.org/)).

To explore the sensitivity of our estimates of R_0 and R_n to assumptions about the proportion initially susceptible, all analyses were repeated assuming that 100% and 50% of each population was susceptible at the start of the first and second waves, respectively.

RESULTS

Proportions infected and clinical attack rates

The proportion of persons with serologic evidence of infection after the first wave of the 1968 pandemic varied from 15% in a North Carolina children's home to 76% in Japanese Self-Defense Forces camps (Web Figure 4). After the second wave, this proportion ranged from 37% in Mombasa, Kenya, to 74% in São Paulo, Brazil. The corresponding susceptible attack rates varied from 19% to 58% during the first wave and from 15% to 50% during the second. Neither the clinical attack rates nor the susceptible attack rate varied markedly with age in the settings for which age-stratified data were available (Web Figures 2 and 3).

Clinical attack rates were generally low (typically 10%–20%) in open settings, except for Kansas City, Missouri, and the Panama Canal Zone, where the attack rates were 39% and 46%, respectively (Web Figure 4). Clinical attack rates were available for only 2 confined settings; these were higher (31% and 36%) than the clinical attack rates in most open settings. Clinical attack rates varied little with age, except in Doncaster, United Kingdom, where they were highest in young to middle-aged adults (Web Figure 3).

Basic and effective reproduction numbers

R_0 and R_n could be estimated from both the final size and the growth rate of the respective epidemics in Kansas City
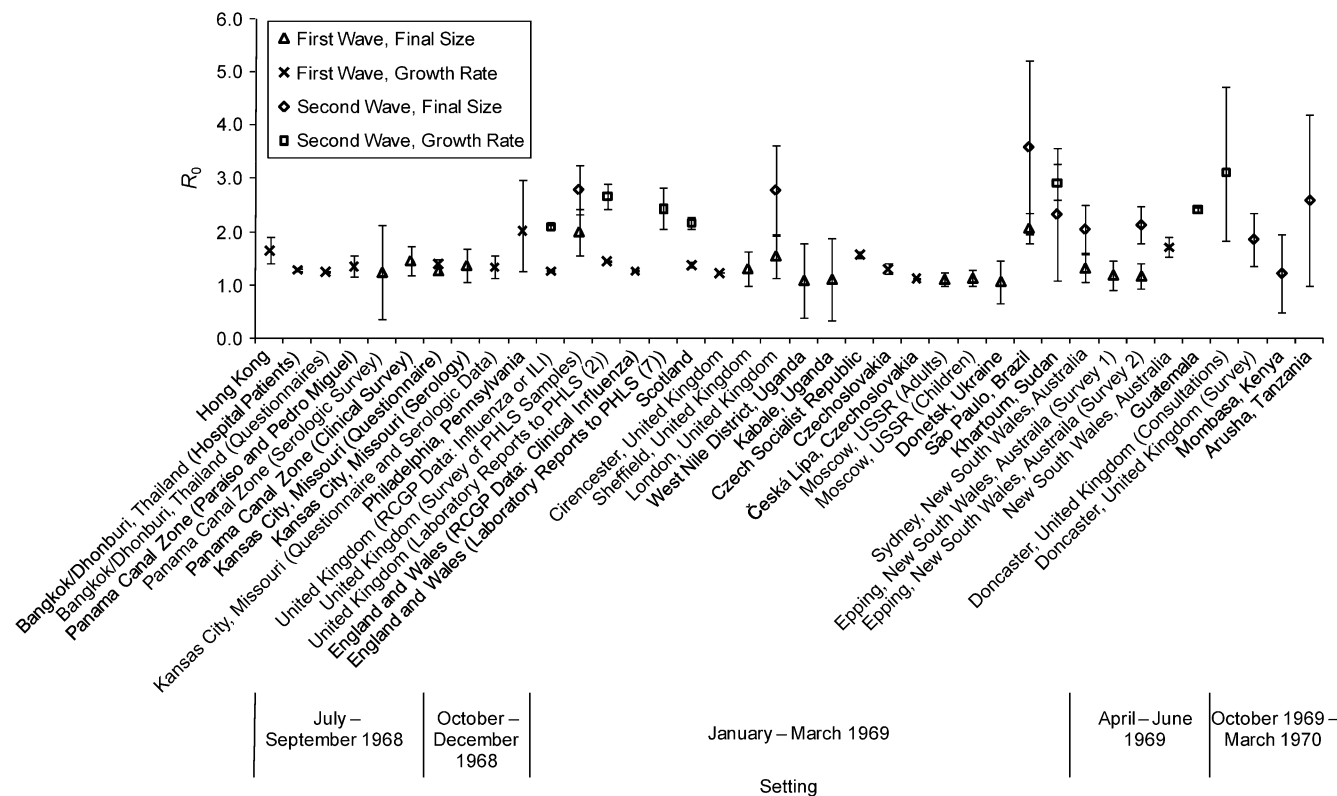
Figure 1. Estimated basic reproduction numbers (R_0) for the 1968 H3N2 influenza pandemic based on the final size or growth rate of the epidemic in open settings. Estimates are arranged in order of occurrence of the first pandemic wave (indicated by the dates at the bottom of the figure), unless only second-wave data are shown. The 2 data sets for Epping, New South Wales, Australia, refer to 2 different retrospective surveys. Data from 5 other districts in Czechoslovakia (Tachov, Most, Pilsen, Ustí nad Labem, and Sokolov), described in the article by Fedová et al. (39), produced results similar to the Czech data shown here (range, 1.10–1.19). ILI, influenza-like illness; PHLS, Public Health Laboratory Service; RCGP, Royal College of General Practitioners; USSR, Union of Soviet Socialist Republics. Bars, 95% confidence interval.

during the first wave and in Khartoum and Doncaster during the second (Tables 1 and 2). In all cases, the 2 methods produced similar estimates. The rest of the estimates of R_0 and R_n are considered irrespective of the method used.

For the first wave, R_n was estimated as 1.06–2.01 and 1.08–1.62 in open and confined settings, respectively (Web Figure 5 (http://aje.oxfordjournals.org/)). The corresponding R_0 estimates, allowing for pre-epidemic immunity as indicated by seropositivity, were 1.06–2.06 and 1.08–1.62 (Figures 1 and 2). The estimates generally appeared similar irrespective of the time of year or location. There were no consistent differences between the estimates of R_0 in open and confined settings.

For the second wave, R_n was estimated as 1.08–2.02 in open settings and as 1.43 (95% confidence interval: 1.23, 1.63) in a single confined setting. The corresponding R_0 estimates for the second wave were 1.21–3.58 (open settings) and 1.86 (95% confidence interval: 1.60, 2.12) (confined setting). In all 10 settings for which R_0 was estimated for both waves, the point estimate for the second wave was higher than that for the first (Table 3). Differences in R_n between waves were variable (e.g., the point estimate for the second wave was higher than that for the first in 7 of 10

data sets), since R_n also depends on the proportion of persons who were susceptible at the beginning of the wave.

Our estimates of R_n based on the growth rate were generally only slightly smaller than the upper bound obtained using the expression $e^{\Lambda T_g}$ (see Web Table (http://aje.oxfordjournals.org/)).

Repetition of the analyses using the alternative assumptions that 100% and 50% of each population were susceptible at the beginning of the first and second waves, respectively, produced R_0 estimates of 1.06–2.01 during the first wave and 1.21–4.22 during the second. The corresponding R_n estimates were 1.06–2.01 and 1.05–2.11 (data not shown). Again, each second-wave R_0 estimate was higher than the corresponding first-wave estimate, while changes in R_n between waves were less consistent.

DISCUSSION

Our results extend knowledge of the H3N2 influenza pandemic, firstly by including data from a much wider geographic range of settings than has been previously analyzed and secondly by estimating transmissibility during both pandemic waves for multiple settings. We found that R_0
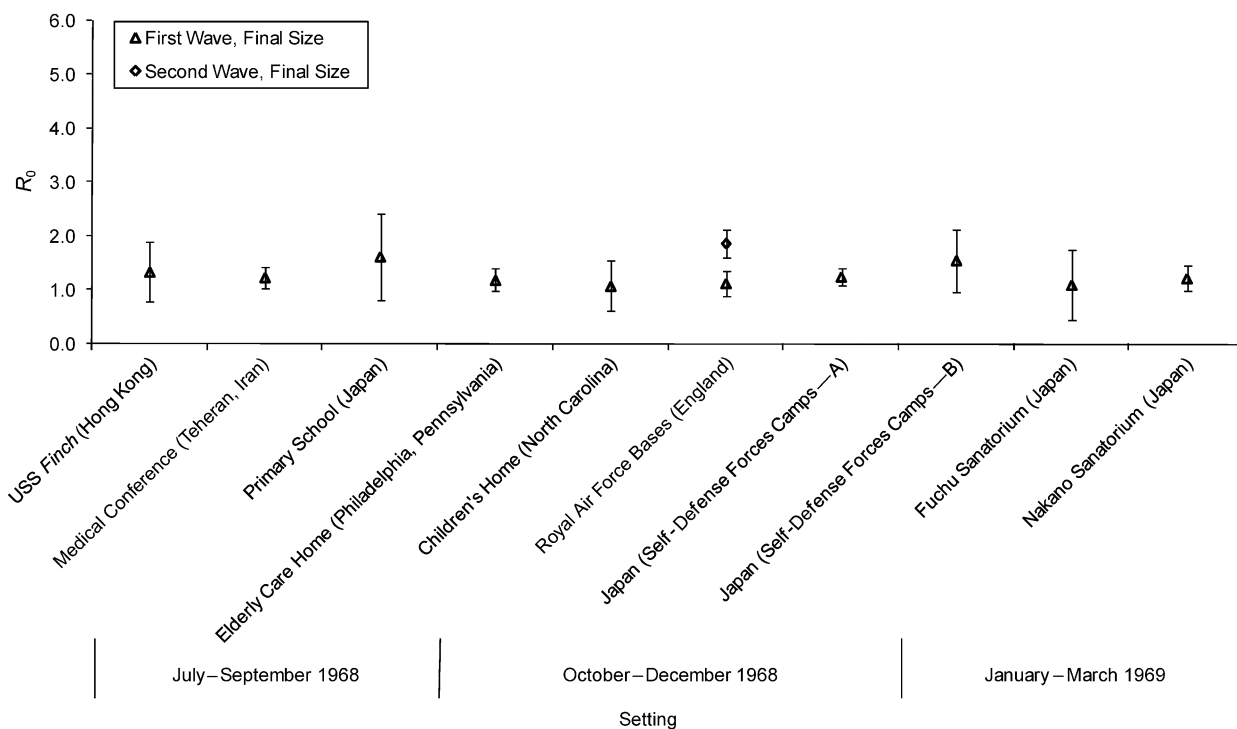
Figure 2. Estimated basic reproduction numbers (R_0) for the 1968 H3N2 influenza pandemic based on the final size or growth rate of the epidemic in confined settings. Estimates are arranged in order of occurrence of the first pandemic wave (indicated by the dates at the bottom of the figure). The 2 data sets for Japanese Self-Defense Forces camps refer to 2 different serologic surveys. Bars, 95% confidence interval.

increased between the 2 waves of the pandemic, being in the ranges 1.06–2.06 and 1.21–3.58 during the first and second waves, respectively. We found little geographic or temporal variation in R_0 or R_n within each wave. In contrast with those found for the 1918 pandemic, our estimates for open and confined settings differed little, perhaps because we defined "confined" rather broadly; for example, primary schools and care homes in 1968/1969 would have been less crowded than the prisons and ships considered for the 1918 pandemic (15).

One of our assumptions was that infection during the first wave conferred immunity during the second. This was based on the facts that 1) the proportion of persons who were seropositive to the prototype Hong Kong virus isolated during the first wave increased between the 2 waves (2–5, 46); 2) hemagglutinin did not evolve significantly between the 2 waves (47, 48); and 3) in 1 study, no person with a ≥4-fold rise in hemagglutination-inhibiting antibody titer during the first wave showed evidence of infection during the second (3).

Our conclusions also depended in part upon the quality of the data assembled. Data quality was difficult to assess for some of the data sets. Many of them appeared to be of high quality, but a few had limitations, such as small sample sizes, unclear clinical case definitions, or low antibody titers in serologic case definitions (Tables 1 and 2). We restricted our estimates of R_0 based on the final epidemic size to data sets with good ascertainment, since these estimates depend on the completeness of case reporting (estimates based on

the growth rate are sensitive to the completeness of reporting only if this changes over time). Clinical data, however, are subject to misclassification and also will exclude asymptomatic infections. This could have caused us to underestimate R_0 based on the final epidemic size from clinical data, if asymptomatically infected persons were infectious.

For a few of the studies, data on the epidemic curve during the early stages of the wave were absent (Web Figure 1). These missing notifications were attributed to background influenza infections or influenza-like illness. The extent to which this assumption was appropriate was difficult to determine for Guatemala, since the outbreak of influenza-like illness was preceded by an epidemic of Venezuelan equine encephalomyelitis (40). Missing data late in the epidemic would not affect estimates based on the growth rate, which use only data from the early stages.

Serologic data, while more specific than clinical data, also have caveats. Firstly, for 6 of the serologic data sets, infection was defined using a relatively low hemagglutination-inhibiting antibody titer (≥1:10 or lower). Secondly, pre-epidemic seropositivity may indicate preexisting cross-reacting antibody rather than infection with H3N2 influenza (3, 24). Either of these factors could have caused us to overestimate the proportion of persons who were immune at either the start or the end of the epidemic wave; the net effect on our estimates of R_0 is difficult to predict.

For example, overestimating the proportion immune at the end of the wave would have caused us to overestimate the final epidemic size and R_0. Overestimating the

Table 3. Changes in the Basic Reproduction Number (R_0) Between Waves of the H3N2 Influenza Pandemic of 1968

Setting	First Wave		Second Wave	
	R_0	95% CI	R_0	95% CI
United Kingdom (RCGP data)	1.26	1.24, 1.28	2.08	2.04, 2.12
United Kingdom (survey of PHLS samples)	2.00	1.57, 2.43	2.78	2.33, 3.23
United Kingdom (laboratory reports to PHLS)	1.44	1.42, 1.46	2.66	2.43, 2.90
England and Wales[a]	1.26	1.24, 1.28	2.42	2.05, 2.82
Scotland	1.37	1.32, 1.42	2.16	2.04, 2.28
Lambeth, London, United Kingdom	1.54	1.13, 1.95	2.77	1.93, 3.61
São Paulo, Brazil	2.06	1.77, 2.35	3.58	1.95, 5.21
Sydney, New South Wales, Australia	1.31	1.04, 1.58	2.04	1.59, 2.49
Epping, New South Wales, Australia	1.16	0.92, 1.41	2.12	1.78, 2.46
Royal Air Force bases, England	1.13	0.89, 1.37	1.86	1.60, 2.12

Abbreviations: CI, confidence interval; PHLS, Public Health Laboratory Service; RCGP, Royal College of General Practitioners.

[a] First-wave estimate was based on clinical data; second-wave estimate was based on laboratory reports.

proportion immune at the start could have led to underestimation of the epidemic size and R_0. It could also have caused us to underestimate the proportion of persons in the population who were responsible for generating the cases during the epidemic, leading to an overestimate in R_0.

We excluded data sets involving vaccinated persons wherever possible. However, the limited quantities of vaccine available during the first wave are not believed to have significantly affected the outbreaks in the United Kingdom or the United States (2, 49). No other large-scale interventions or behavior changes were mentioned in the source papers (where data referred to intervention trials, we included only the control groups), but people may have reactively reduced their social mixing, as apparently happened during the 1918 pandemic (50). Successful interventions, if implemented, would have reduced the epidemic size, leading us to underestimate R_0 on this basis. However, they probably would have been introduced too late to affect our estimates based on the growth rate, which used only data from the epidemic's early stages.

To our knowledge, only 1 previous study has assessed the transmissibility of H3N2 influenza during both pandemic waves (19). Using general practice consultation data from England and Wales, Hall et al. (19) found that R_n increased slightly from 1.28 during the first wave to 1.56 during the second. This is broadly consistent with our estimates of R_n for this setting (nationally and subnationally), which ranged from 1.10 to 1.30 during the first wave and from 1.19 to 2.02 during the second. While we estimated that R_0 increased between waves in all settings for which data on both waves

were available, it is unclear whether this conclusion is generalizable to other settings: It is possible that in some settings, only 1 wave occurred or a second wave occurred but was not reported.

Changes in transmissibility have been examined for successive waves of the 1918 H1N1 pandemic. In Geneva, Switzerland, R_0 was estimated to increase from 1.49 during the first wave to an R_n of 3.75 during the second wave (14). In Scandinavia, transmissibility decreased between waves (e.g., from 2.2–3.0 for R_0 during the first wave to 1.2–1.3 for R_n during the second in Copenhagen, Denmark (16)), which could be attributable to reductions in both the susceptible population and R_0. Other studies of this pandemic found that R_0 decreased (e.g., from 2.1 to 1.8 to 1.5 in successive waves in England and Wales (13)), showed no clear pattern (12, 13), or remained relatively unchanged (15).

The increases in R_0 between successive waves of the H3N2 pandemic suggested here might be attributable to at least 2 factors. First, they could be related to molecular changes in the virus; for example, drift in the neuraminidase between the 2 waves has been reported (47, 48) and could perhaps be associated with increased transmissibility. Second, they could be related to the timing of the respective outbreaks. For example, the first wave in the United Kingdom began just before Christmas, whereas the larger outbreaks of the second wave in the United Kingdom and the first wave in the United States began earlier in the year, before holidays would have interrupted contact between people at schools and workplaces. Immunity generated during the unusually large first wave in the United States probably helped to limit the attack rates there during the second wave. It is interesting that, in Europe and Asia, the majority of influenza-related deaths occurred during the second wave, while in North America the first wave had the greater mortality impact (48). We could not assess whether these differences were reflected in changes in R_0 between the 2 waves, since no suitable second-wave data were identified for any American setting.

It is unlikely that the apparent increase in R_0 between waves was due to increased ascertainment during the second wave (e.g., due to greater awareness of the virus), since increases were observed even using serologic data from samples submitted for other tests (2–4), for which ascertainment is unlikely to vary between waves.

Our estimates of R_0 are lower than many previous estimates for the 1918 (10–16) and 1957 (12, 13, 17) pandemics, which is consistent with the correspondingly smaller size of the 1968 pandemic. Our estimates of R_0 for the first wave of the H3N2 pandemic are also lower than the 2 previous estimates for this wave (20, 21), which were derived from models describing the global spread of influenza; Rvachev and Longini (20) and Longini et al. (51) estimated R_0 as 3.10, and Cooper et al. (21) estimated it as between 0.5–1.5 and 2.5–3.5. Both sets of investigators assumed that approximately 60% of the global population was initially susceptible. We generally assumed that the proportion susceptible was higher than this, based on the available serologic data for each setting. Using the figure of 60% for the data sets for which this was possible would produce estimates of R_0 for the first wave of 1.76–3.35,

consistent with these previous estimates. Our estimates of R_n were close to the upper bounds (45); consequently, if our assumptions about the proportion susceptible are correct, our estimates of R_0 are probably not underestimates. In fact, if the generation time of H3N2 pandemic influenza was shorter than the 4 days we assumed (shorter generation times have been assumed for other influenza viruses (52) and estimated for H1N1 influenza (53)), the R_0 would be even lower than estimated here.

R_0 for the second pandemic wave has been estimated as 2.2 (12) and R_n as 1.85 (12), 1.8 (13), or 1.56 (19). Other analyses of the second wave implied an R_0 of 3.5 in England and Wales and an R_0 of 3.5 or 4.9 in Greater London (11, 18; Ben Cooper, Health Protection Agency, United Kingdom, unpublished observations). Most of our R_0 estimates for the second wave lie within the range of these previous estimates.

It is possible that H1N1 influenza will cause a second wave of infection, and it is difficult to predict whether the virus will continue to behave as it has done thus far. Our results indicate that pandemic influenza viruses may become more transmissible between successive waves, and this possibility should be considered in mitigation strategies.

Editor's note: *Reference 54 is cited in the legend of Web Figure 3 (http://aje.oxfordjournals.org/).*

ACKNOWLEDGMENTS

REFERENCES

1. Taylor MP. Influenza 1969–70. Incidence in general practice based on a population survey. *J R Coll Gen Pract.* 1971; 21(102):17–22.
2. Miller DL, Pereira MS, Clarke M. Epidemiology of the Hong Kong-68 variant of influenza A2 in Britain. *Br Med J.* 1971; 1(5747):475–479.
3. Miller DL, Reid D, Daimond JR, et al. Hong Kong influenza in the Royal Air Force 1968–70. *J Hyg (Lond).* 1973;71(3): 535–547.
4. Candeias JA, Pereira MS. The measurement by serological means of the impact of the Hong Kong/68 influenza virus on a population. *Rev Saude Publica.* 1972;6(1):85–88.
5. Gill PW, Murphy AM. The incidence of A2-Hong Kong infections in blood donors during the winter of 1970. *Med J Aust.* 1972;2(5):242–246.
6. Gill PW, Babbage NF, Gunton PE, et al. Did the Asian virus protect us from Hong Kong influenza? *Med J Aust.* 1971;2(1):53–54.
7. Weekly update. *BMJ.* 1969(1):130, 194, 262, 325, 452, 521, 585, 652, 724, 790, 852; 1969(2):196, 257, 321, 391, 456; 1970(1): 373, 440, 699; 1970(2):120.
8. Weekly update. *Commun Dis Scotl.* 1969:1–24, 1969:49–53; 1970:1–16.
9. Salim AR. Hong Kong influenza in the Sudan. *Bull World Health Organ.* 1971;44(5):713–716.
10. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. *Nature.* 2004;432(7019):904–906.
11. Spicer CC, Lawrence CJ. Epidemic influenza in Greater London. *J Hyg (Lond).* 1984;93(1):105–112.
12. Gani R, Hughes H, Fleming D, et al. Potential impact of antiviral drug use during influenza pandemic. *Emerg Infect Dis.* 2005;11(9):1355–1362.
13. Viboud C, Tam T, Fleming D, et al. Transmissibility and mortality impact of epidemic and pandemic influenza, with emphasis on the unusually deadly 1951 epidemic. *Vaccine.* 2006;24(44–46):6701–6707.
14. Chowell G, Ammon CE, Hengartner NW, et al. Transmission dynamics of the great influenza pandemic of 1918 in Geneva, Switzerland: assessing the effects of hypothetical interventions. *J Theor Biol.* 2006;241(2):193–204.
15. Vynnycky E, Trindall A, Mangtani P. Estimates of the reproduction numbers of Spanish influenza using morbidity data. *Int J Epidemiol.* 2007;36(4):881–889.
16. Andreasen V, Viboud C, Simonsen L. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. *J Infect Dis.* 2008;197(2):270–278.
17. Longini IM Jr, Halloran ME, Nizam A, et al. Containing pandemic influenza with antiviral agents. *Am J Epidemiol.* 2004; 159(7):623–633.
18. Spicer CC. The mathematical modelling of influenza epidemics. *Br Med Bull.* 1979;35(1):23–28.
19. Hall IM, Gani R, Hughes HE, et al. Real-time epidemic forecasting for pandemic influenza. *Epidemiol Infect.* 2007;135(3): 372–385.
20. Rvachev LA, Longini IM Jr. A mathematical model for the global spread of influenza. *Math Biosci.* 1985;75(1):3–22.
21. Cooper BS, Pitman RJ, Edmunds WJ, et al. Delaying the international spread of pandemic influenza [electronic article]. *PLoS Med.* 2006;3(6):e212.
22. Zachary IG, Johnson KM. Hong Kong influenza in the Panama Canal Zone. First epidemic by a new variant in the Western Hemisphere. *Am J Trop Med Hyg.* 1969;18(6):1048–1056.
23. Davis LE, Caldwell GG, Lynch RE, et al. Hong Kong influenza: the epidemiologic features of a high school family study analyzed and compared with a similar study during the 1957 Asian influenza epidemic. *Am J Epidemiol.* 1970;92(4):240–247.
24. Machin SJ, Potter CW, Oxford JS. Changes in the antibody status of a population following epidemic infection by influenza virus A2-Hong Kong-1-68. *J Hyg (Lond).* 1970;68(3): 497–504.

25. Montefiore D, Drozdov SG, Kafuko GW, et al. Influenza A2-Hong Kong-68 virus in Uganda. *Trop Geogr Med*. 1970;22(4):452–458.

26. Montefiore D, Drozdov SG, Kafuko GW, et al. Influenza in East Africa, 1969–70. *Bull World Health Organ*. 1970;43(2):269–273.

27. Salim AR. Serological evidence of A2 Hong Kong influenza in Sudan. *Trop Geogr Med*. 1974;26(2):210–213.

28. Wiebenga NH, Kundin WD, French GR, et al. Epidemic influenza on a naval vessel in Hong Kong, 1968. *Am J Epidemiol*. 1970;91(1):59–67.

29. Fukumi H. Summary report on Hong Kong influenza in Japan. *Bull World Health Organ*. 1969;41(3):353–359.

30. Sonoguchi T. Haemagglutination-inhibiting antibody response to and efficacy of inactivated Hong Kong influenza vaccine. *Bull World Health Organ*. 1969;41(3):517–523.

31. Sanders DY, Carroll NB, Jeffreys LU, et al. Outbreak of influenza A2 (Hong Kong strain) in a children's home. *South Med J*. 1970;63(4):414–416.

32. Solov'ev VD. The results of controlled observations on the prophylaxis of influenza with interferon. *Bull World Health Organ*. 1969;41(3):683–688.

33. Gill PW, Babbage NF, Gunton PE, et al. Hong Kong influenza: the coming winter. *Med J Aust*. 1970;1(8):393–394.

34. Saenz AC, Assaad FA, Cockburn WC. Outbreak of A2-Hong Kong-68 influenza at an international medical conference. *Lancet*. 1969;1(7585):91–93.

35. Satz J, Prier JE, Riley R, et al. Epidemiological and biological characteristics of the Hong Kong influenza epidemic in Pennsylvania during 1968–1969. *Am J Public Health*. 1970;60(12):2197–2207.

36. Wiebenga NH, Chang WK, French GR, et al. Epidemic disease in Hong Kong, 1968, associated with an antigenic variant of Asian influenza virus. *Am J Public Health Nations Health*. 1970;60(9):1806–1812.

37. Thongcharoen P, Thepitaksa M, Prakobpol C, et al. 1968—outbreak of influenza in Thailand: epidemiological and laboratory investigations. *J Med Assoc Thai*. 1969;52(9):724–736.

38. Hope-Simpson RE. First outbreak of Hong Kong influenza in a general practice population in Great Britain. A field and laboratory study. *Br Med J*. 1970;3(5714):74–77.

39. Fedová D, Drasnar M, Strnad P, et al. Hong Kong influenza in Czechoslovakia, 1969: a preliminary surveillance report. *Bull World Health Organ*. 1969;41(3):367–373.

40. Influenza—Guatemala 1969. *MMWR Morb Mortal Wkly Rep*. 1970;19:107.

41. Hilborn R, Mangel M. *The Ecological Detective Confronting Models With Data (Paper): Confronting Models With Data*. Princeton, NJ: Princeton University Press; 1997.

42. Becker N. *Analysis of Infectious Disease Data*. London, United Kingdom: Chapman and Hall Ltd; 1989.

43. Wearing HJ, Rohani P, Keeling MJ. Appropriate models for the management of infectious diseases [electronic article]. *PLoS Med*. 2005;2(7):e174.

44. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases [electronic article]. *PLoS Med*. 2008;5(3):e74.

45. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc Biol Sci*. 2007;274(1609):599–604.

46. Stuart-Harris C. Epidemiology of influenza in man. *Br Med Bull*. 1979;35(1):3–8.

47. Lindstrom SE, Cox NJ, Klimov A. Genetic analysis of human H2N2 and early H3N2 influenza viruses, 1957–1972: evidence for genetic divergence and multiple reassortment events. *Virology*. 2004;328(1):101–119.

48. Viboud C, Grais RF, Lafont BA, et al. Multinational impact of the 1968 Hong Kong influenza pandemic: evidence for a smoldering pandemic. *J Infect Dis*. 2005;192(2):233–248.

49. Murray R. Production and testing in the USA of influenza virus vaccine made from the Hong Kong variant in 1968–69. *Bull World Health Organ*. 1969;41(3):495–496.

50. Bootsma MC, Ferguson NM. The effect of public health measures on the 1918 influenza pandemic in U.S. cities. *Proc Natl Acad Sci U S A*. 2007;104(18):7588–7593.

51. Longini IM Jr, Fine PE, Thacker SB. Predicting the global spread of new infectious agents. *Am J Epidemiol*. 1986;123(3):383–391.

52. Halloran ME, Ferguson NM, Eubank S, et al. Modeling targeted layered containment of an influenza pandemic in the United States. *Proc Natl Acad Sci U S A*. 2008;105(12):4639–4644.

53. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. *Science*. 2009;324(5934):1557–1561.

54. Hope-Simpson RE. Age and secular distributions of virus-proven influenza patients in successive epidemics 1961–1976 in Cirencester: epidemiological significance discussed. *J Hyg (Lond)*. 1984;92(3):303–336.