Review

Spanish Flu, Asian Flu, Hong Kong Flu, and Seasonal Influenza in Japan under Social and Demographic Influence: Review and Analysis Using the Two-Population Model

Hiroshi Yoshikura*

National Institute of Infectious Diseases, Tokyo 162-8640, Japan

(Received September 25, 2013. Accepted January 6, 2014)

CONTENTS:

1. Introduction
2. Review
 - 2-1. Spanish flu (1918–1920)
 - 2-1-1. The first wave (August 1918–July 1919)
 - 2-1-2. The second wave (October 1919–July 1920)
 - 2-1-3. The third wave (August 1920–July 1921)
 - 2-2. Asian flu (1957–1958)
 - 2-3. Hong Kong flu (1968–1969)
 - 2-4. Seasonal influenza
3. Analysis using the two-population model
 - 3-1. Spanish flu
 - 3-1-1. Time course of the epidemic
 - 3-1-2. Examining the applicability of the two-population hypothesis
 - 3-2. Asian flu
 - 3-2-1. Time course of the epidemic
 - 3-2-2. Examining the applicability of the two-population hypothesis
 - 3-3. Hong Kong flu
 - 3-4. Seasonal influenza
 - 3-4-1. Epidemiological considerations
 - 3-4-2. Examining the applicability of the two-population hypothesis
4. Discussion

SUMMARY: When cumulative numbers of patients (X) and deaths (Y) associated with an influenza epidemic are plotted using the log-log scale, the plots fall on an ascending straight line generally expressed as $\log Y = k(\log X - \log N_0)$. For the 2009 H1N1 influenza pandemic, the slope k was ~ 0.6 for Mexico and ~ 2 for other countries. The two-population model was proposed to explain this phenomenon (Yoshikura H. *Jpn J Infect Dis.* 2012;65:279-88; Yoshikura H. *Jpn J Infect Dis.* 2009;62:411-2; and Yoshikura H. *Jpn J Infect Dis.* 2009;62:482-4). The current article reviews and analyzes previous influenza epidemics in Japan to examine whether the two-population model is applicable to them. The slope k was found to be ~ 2 for the Spanish flu during 1918–1920 and the Asian flu during 1957–1958, and ~ 1 for the Hong Kong flu and seasonal influenza prior to 1960–1961; however, k was ~ 0.6 for seasonal influenza after 1960–1961. This transition of the slope k of seasonal influenza plots from ~ 1 to ~ 0.6 corresponded to the shift in influenza mortality toward the older age groups and a drastic reduction in infant mortality rates due to improvements in the standard of living during the 1950s and 1960s. All the above observations could be well explained by reconstitution of the influenza epidemic based on the two-population model.

1. Introduction

Large-scale influenza epidemics have occurred in Japan in the past, including the Spanish flu during 1918–1920, Asian flu during 1957–1958, Hong Kong flu during 1968–1969, and 2009 H1N1 pandemic during 2009–2010. While each of these epidemics had its own unique characteristics, the Spanish flu has been cited as the worst. The past epidemics are valuable sources of information on how new strains of influenza virus originate and spread among human populations, how they cause fatality in humans, and how they eventually disappear. The present paper reexamines published data on these epidemics and seasonal influenza from the

point of view of case fatality, and particularly with regard to the applicability of two-population hypothesis (1).

2. Review

Documents pertaining to the Spanish, Asian, and Hong Kong influenza epidemics of Japan are reviewed below, with a greater focus on the Spanish flu, because this epidemic occurred not long after the Meiji Restoration and even before the discovery of the influenza virus.

2-1. Spanish flu (1918–1920)

The Spanish flu ravaged Japan from 1918 to 1920. The data compiled by the Ministry of Home Affairs, Government of Japan (2) are surprisingly detailed and comprehensive, considering that the compilation was done before the discovery of the influenza virus.

The surveillance began at the prefecture level in August 1918. On December 27, 1919, the Director

*Corresponding author: Mailing address: Department of Food Safety, Ministry of Health, Labour and Welfare, 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-8916, Japan. E-mail: yoshikura-hiroshi@mhlw.go.jp

General of Hygiene Bureau (Eisei-Kyoku), Ministry of Home Affairs (Naimu-Sho) ordered the governors of all prefectures to document and notify influenza cases every 10 days, outlining the epidemic situation; the number of patients and deaths; the residence, age, and occupation of the patients; and regions in the prefecture most severely hit by the epidemic. The clinical symptoms mentioned in the notification included inflammation of respiratory organs such as larynx, nasal cavity, pharynx, trachea, and bronchus; pneumonia and pleurisy following tracheitis or bronchitis; circulatory complications such as bradycardia or tachycardia, hypotension, and cyanosis; bleeding tendency; digestive tract complications such as vomiting, abdominal pain, and bloody stool; neurological complications such as headache, insomnia, neuralgia, arthralgia, severe general malaise, neuritis, encephalomyelitis, encephalitis, and meningitis; renal symptoms such as feverish proteinuria and nephritis; and rashes.

The document states that the epidemic occurred in three waves, with the first wave occurring during August 1918–July 1919, the second wave during October 1919–July 1920, and the third wave during August 1920–July 1921. The numbers of patients reported in the three waves were 21,168,398; 2,412,097; and 224,178, respectively, with 257,363; 127,666; and 3,698 reported deaths for the respective waves. Case-fatality rates of 1.22%, 5.29%, and 1.65% were calculated for the respective waves.

2-1-1. The first wave (August 1918–July 1919)

The epidemic began in August 1918. By January 15, 1919, approximately 19,236,000 individuals (approximately 1/3rd of the total Japanese population) were infected, and 204,000 deaths (3.58 per 1,000 population) were reported. In several prefectures, the epidemic began in cities with easy access, ravaged them in a few days, and then spread to the surrounding communities. Schools and manufacturing factories closed down one after another. The document states that the case-fatality rate increased gradually from the initial 1%–3% in 1918 to nearly 5% in April 1919. While fatality was initially limited to infants and elderly, as the epidemic progressed, healthy people succumbed to severe complications such as pneumonia.

2-1-2. The second wave (October 1919–July 1920)

The infected patients were chiefly those who had been spared in the first wave. The individuals who had been infected in the first wave showed milder symptoms, and prefectures that were affected in the first wave were less affected this time. Although the number of patients was smaller than that in the first wave, the calculated case-fatality rate was as high as 10% in March and April 1920.

2-1-3. The third wave (August 1920–July 1921)

The characteristics of the epidemic features and clinical symptoms were indistinguishable from common cold.

2-2. Asian flu (1957–1958)

According to a publication by Japan Public Health Association (3), the epidemic was first observed in May 1957 as influenza outbreaks in primary schools in Tokyo and Kyoto. Within 2 weeks, the epidemic spread to 25 prefectures. Schools were closed one after another; for example, by June 19, 1957, 5,339 schools

were affected and 1,763 schools were temporarily closed, and from August 1957 to November of the same year, 5,525 schools were affected and 2,197 schools were temporarily closed. In 1957, a total of 983,105 infections and 7,735 deaths were reported, with a calculated case-fatality rate of 0.8%. Half of the Japanese population was estimated to have been affected by this epidemic, which was caused by influenza virus A2 strain A/Asia/type 57.

2-3. Hong Kong flu (1968–1969)

According to the document published by Japan Public Health Association (4), Hong Kong influenza A2 (AHK) was first introduced into Japan by the Israeli crew of a cargo ship on August 1, 1968. On September 5, the first Japanese case of AHK infection was detected in Osaka, followed by reports of sporadic cases in other cities such as Tokyo, Osaka, and Nagoya. The numbers of patients started increasing in early October, and the epidemic continued until January of the following year. The Hong Kong flu epidemic was preceded by an epidemic of influenza B, which persisted during the early phase of the Hong Kong flu epidemic. The total number of patients and reported deaths during the epidemic (week 41 of 1968 to week 16 of 1969) were 127,086 and 985, respectively, with a calculated case-fatality rate of 0.8%. During the epidemic, the isolation ratio of AHK versus influenza B was found to be 141:130; therefore, it was possible that a substantial fraction of the patients were infected with the non-epidemic influenza virus B (4).

2-4. Seasonal influenza

Mortality data for influenza is available since 1900, with a short interruption corresponding to the Second World War. At present, the mortality data are available with Vital Statistics in Japan, whose history is outlined in their webpage (<http://www.stat.go.jp/data/chouki/02exp.htm> [in Japanese]). Morbidity data for influenza are available subsequent to 1947; the morbidity data of all infectious diseases are available in Health and Welfare Statistics of Communicable Disease and Food Poisoning, Japan (Patients and deaths of infectious diseases and food poisoning [1986–1999], Ministry of Health, Labour and Welfare [in Japanese]).

3. Analysis using the two-population model

The case-fatality rate (R) is the number of deaths (Y) divided by the number of infected individuals (X), i.e., $R = Y/X$. R has been regarded as constant throughout an epidemic because R is determined by the balance between pathogen virulence and host sensitivity, which is unique to the pathogen-host pair. Actually, R has remained constant during the epidemics of several infectious diseases, including the cholera epidemic in Haiti or the epidemic of hand, foot, and mouth disease in China (1). However, for the 2009 H1N1 influenza epidemic that originated in Mexico, R changed over time, following a kinetics generally expressed as $\log Y = k(\log X - \log N_0)$, where k is the slope and N_0 , the point where the plot (straight line) intersects the X -axis (note: when $k = 1$, $R = 1/N_0$) (5).

If the case-fatality rate R remains constant, k is 1, because $R = Y/X$ is equivalent to $\log Y = \log X + \log R$. The slope k was ~ 0.6 in Mexico where the epidemic

originated and ~ 2 in countries where the influenza epidemic occurred secondarily due to import of the causative virus (5). The observation made for the 2009 H1N1 epidemic was therefore clearly anomalous. This anomalous situation could be explained by the “two-population” model, which postulates two different populations where the virus spreads with different speeds and death rates (6). It has to be reminded here that the equation above-mentioned was proposed to explain only the initial phase of the epidemic.

The present analysis was conducted to examine whether a phenomenon similar to the one experienced with the 2009 H1N1 epidemic could be observed in the previous influenza epidemics in Japan, and to examine whether the two-population hypothesis is applicable in such situation.

3-1. Spanish flu

3-1-1. Time course of the epidemic

Figure 1A shows the number of patients and reported deaths every half month from the second half of January 1919 to the end of June 1919. Figure 1B shows the plot of patients and deaths each month for the second (November 1919–December 1919, square symbol) and third (January 1920–July 1921, circle symbol) waves.

Figure 1C shows the log-log plot of the cumulative number of patients (horizontal axis) versus cumulative number of deaths (vertical axis) for the three epidemic waves. The slope k of the plots for the first (open triangles) and second (open squares) waves was ~ 2 ; and for the third wave (open circles), which was described as “indistinguishable” from the common cold, the slope was ~ 0.75 .

In Fig. 1C, the plots for Kanagawa and Tokyo are

Fig. 1. Spanish flu epidemic nationwide. (A and B) Time course of patient number and death number reported every half month (A) or every month (B). The data are all derived from “Table 1: the first wave (from the second half of January 1918 to the first half of July 1918),” “Table 2: the second wave (January 1920–July 1920),” and “Table 3: the third wave (August 1920–July 1921)” in “Numbers of patients and deaths in the epidemic influenza” (2). Open symbols indicate number of patients and closed symbols number of deaths. Cross symbols indicate the case-fatality rate (%) in a half month (A) or a month (B) at each point. Vertical axis, number of patients, number of deaths, and % deaths; horizontal axis, number of half months elapsed from the latter half of January 1919 for panel A; and number of months after December 1919 for panel B. (C) Log-log plot of cumulative number of patients (X-axis) vs. cumulative number of deaths (Y-axis). The dotted line indicates a straight line with slope $k = 1$ (45° slope). Open triangles, open squares, and open circles represent the first, the second, and the third waves, respectively. Closed triangles and closed squares correspond to the first and the second waves, respectively, in Tokyo. Shaded triangles and shaded squares correspond to the first and the second waves in Kanagawa. The data for the first wave of Japan as a whole was data from August 1918 to 1919, while those for individual prefectures were those from January 1919 to June 1919. Approximated correlation lines were drawn using the “power approximation” in Excel file.

Fig. 2. Log-log plot of cumulative number of patients (X-axis) vs. cumulative number of deaths (Y-axis) for each prefecture (not all the prefectures are shown). The data for individual prefectures are those from January 1919 to June 1919. Approximated correlation lines were drawn using the “power approximation” in Excel file.

A	1st wave	slower spread/lower death rate Population A		quicker spread/higher death rate Population B		A+B		
	time	patients	deaths	patients	deaths	patients	deaths	d/p (%)
	t1	375000	375	31250	3125	406250	3500	0.9
	t2	750000	750	125000	12500	875000	13250	1.5
	t3	1500000	1500	500000	50000	2000000	51500	2.5
		M=2	D=0.1%	M=4	D=10%			

B	2nd wave	slower spread/lower death rate Population A		quicker spread/higher death rate Population B		A+B		
	time	patients	deaths	patients	deaths	patients	deaths	d/p (%)
	t1	250000	250	40000	4000	290000	4250	1.5
	t2	500000	500	160000	16000	760000	16500	2.2
	t3	1000000	1000	640000	64000	1640000	65000	4
		M=2	D=0.1%	M=4	D=10%			

C	3rd wave	quicker spread/lower death rate (A)		slower spread/higher death rate (B)		A+B		
	time	patients (A)	deaths (A)	patients (B)	deaths (B)	patients	deaths	Case-fatality rate (%)
	t1	1600	2	3000	300	4600	302	6.5
	t2	8000	8	6000	600	14000	608	4.3
	t3	40000	40	12000	1200	52000	1240	2.4
	t4	200000	200	24000	2400	224000	2600	1.2
		M=5	D=0.01%	M=2	D=10%			

Fig. 3. Tables used for reconstitution of the first wave (A), the second wave (B), and the third wave (C) of Spanish flu. “A + B” means the addition of the corresponding figures for populations A and B. t_1 , t_2 , and t_3 indicate time, which do not necessarily proportional to the physical time. M and D indicate the multiplication rate of the patient number and death rate (%), respectively. “Case-fatality rate” is “deaths” divided by “patients” (%).

also shown; the slope k was ~ 2 for the first and second waves in Kanagawa. The slope k of the first wave in Tokyo was, however, ~ 1 , while that of the second wave was ~ 2 .

Figure 2 shows the log-log plots for some of the other prefectures. The following observations merit mention:

1. In general, the slope for the first wave was very

steep (as high as ~ 4) compared with that for the second wave. The increased steepness of the slope reflects a situation where the propagation of the virus has slowed down, but infected patients continue to die. This indicates that data collection for the first wave started toward the end of the epidemic wave.

2. The straight line plots (with a slope of ~ 2) for the first and second waves in Japan as a whole (Fig. 1C; open triangles and open squares for the first and second waves, respectively) actually consist of similar but divergent plots of epidemics at the prefecture level, which began with different timings (2). Each plot for prefectures in turn consists of plots for townships and villages, and, as discussed below, all the plots with a slope of ~ 2 will be finally disintegrated into smaller plots with a slope of ~ 1 .

3-1-2. Examining the applicability of the two-population hypothesis

As previously proposed (6), log-log plots with slopes that deviate from 1 can be reconstituted by postulating two populations with differences in the virus propagation rate (M) and death rate (D). The death rate D refers to the case-fatality rate unique to the hypothetical subpopulations in the model. The virus propagation rate M refers to the fold-multiplication of patient numbers from time t_i to time t_{i+1} in the model; examples can be found in Fig. 3.

In the case of 2009 H1N1 epidemic, a slope k of > 1

could be explained by postulating two human subpopulations, a normal majority and a minority population where the virus spreads more rapidly with a higher mortality rate than in the normal majority population. Figure 3 shows the tables used for reconstitution of the three waves of the Spanish flu based on the “two-population” model.

The first and second waves, with a slope k of ~ 2 , were simulated by postulating population A, a majority where the virus spreads with propagation speed $M = 2$ and death rate $D = 0.1\%$, and population B, a minority where the virus spreads more rapidly ($M = 4$) with a higher death rate ($D = 10\%$). The ratio of population A to population B was set to 10:1 (375,000 vs. 31,250) at time t_1 for the first wave and 6:1 (250,000 vs. 40,000) for the second wave (Fig. 3A and 3B). In this case, time expressed as t_1 , t_2 , and so forth is not meant to be proportional to physical time. The reconstitution was seen to fit well with the actual plots (Fig. 4A and 4B). However, the above-mentioned reconstitution was done by trial and error, and a similar straight line can be obtained using slightly different combinations of parameter values through fine-tuning, as detailed (1). In Fig. 4A,

Fig. 4. Log-log plot of cumulative number of patients (X-axis) vs. cumulative number of deaths (Y-axis) in the reconstituted Spanish flu. (A) The first wave, (B) the second wave, and (C) the third wave. Open symbols, plots of the observed data (for the first wave, data used were those from January 1919 to June 1919, while data used for in Fig. 1C were those from August 1918 to June 1919). Closed symbols, plots of the reconstituted data. (D) Evolution of ratio between population B (vertical axis) vs. population A (horizontal axis) among patients (open symbols) or among deaths (closed symbols) in the reconstituted epidemic deduced from the tables in Fig. 3. Triangles, squares, and circles correspond to the first, second, and third waves, respectively. If the ratio between population A and population B remains, the plot will on an ascending line whose slope is 45° .

the plots for the model subpopulations A and B in the first wave of the epidemic are shown. The slopes of both plots equaled 1; in other words, if the prefecture is divided into its smallest units, the slope of all plots will become 1.

The third wave with a slope k of ~ 0.75 was reconstituted by postulating two populations of roughly equal size, population A where the virus spreads more rapidly ($M = 5$) with a lower death rate ($D = 0.1\%$) and population B where the virus spreads comparatively slowly ($M = 2$) but with a higher death rate ($D = 10\%$) (Fig. 3C). This instance is compatible with a situation where the spread of the Spanish flu has decelerated because a majority of the population (population B) has acquired immunity to the virus, and a new seasonal influenza virus strain with lower virulence has started spreading quickly (population A). The reconstituted plots fit well with the actual data, as shown in Fig. 4C.

Figure 4D was derived from the tables in Fig. 3 to depict the possible evolutionary routes leading to the relative abundance of population A (X-axis) versus population B (Y-axis) among patients (open symbols) and death cases (closed symbols). For the first and second waves (triangles and squares, respectively), the slope of the plot was steeper than 45° , indicating that population B increased more rapidly than population A. For the third wave (circle symbols), the slope of the plot was less than 45° , indicating that population A became increasingly predominant over time.

Epidemics in individual prefectures (Fig. 2) can be similarly reconstituted, with the exception of the first wave in Tokyo (Fig. 1C). While the second wave in Tokyo was easily reconstituted (Fig. 5A, lower table and Fig. 5B, right panel), reconstitution of the first wave presented difficulties. If the death rate in population B was set to 10% as in the other prefectures, reconstitution was possible only if the spread of the Spanish flu matched that of the seasonal flu (Fig. 5A, upper table and Fig. 5B, left panel). An alternate possibility is that the death rate in the first wave in Tokyo was constantly 1%. No available data, however, suggest this exceptional situation in Tokyo; the exception includes an observation by Hayami, who extensively surveyed newspaper articles (7). He noted that newspapers in Tokyo, as opposed to the other prefectures, were surprisingly silent on the Spanish flu initially. The first wave of the Spanish flu in Tokyo may have begun insidiously rather than explosively.

As proposed by Ewald (8), low virulence offers advantages over high virulence in the propagation of pathogens, because hosts infected with virulent strains are immobilized and present less opportunities for viral propagation; a pathogen with high virulence can prevail only if it has its host in easy access. The challenge then was to identify the Japanese communities in 1918–1919 that were likely associated with population B.

When the Spanish influenza virus reached Japan in 1918, the prevailing conditions were ideal for the spread

Fig. 5. Reconstituted first and second waves of Spanish flu in Tokyo. (A) Tables used for the reconstitution. (B) Log-log plots of cumulative number of patients (X-axis) vs. cumulative number of deaths (Y-axis) in the reconstituted first wave (left panel) and in the reconstituted second wave (right panel).

Fig. 6. Asian flu epidemic (June 1957 to June–March 1958) and seasonal influenza epidemics before and after the epidemic. Data of deaths were derived from Vital Statistics in Japan, “List of Statistical Surveys conducted by Ministry of Health, Labour and Welfare,; “Table: Deaths from causes (abbreviated list) by sex and month of occurrence: for all Japan (1968)” and data of patients from Health and Welfare Statistics of Communicable Disease and Food Poisoning Japan: “Statistics of Transmissible Diseases; Table: Number of cases, case rates (per 100,000 population) of each disease (reportable) by month.” (A) Time course of number of patients (plots connected by a solid line) and deaths (plots connected by a broken line) reported monthly. The horizontal arrow indicates the duration of the epidemic identified in the document (3). Vertical axis, number of patients and number of deaths per month; horizontal axis, number of months elapsed from January 1956 (open squares, January 1956–August 1956; triangles, September 1956–September 1957; open circles, October 1957–September 1958; closed squares, October 1958–December 1959). (B) The log-log plots of cumulative number of deaths (Y-axis) vs. cumulative number of patients (X-axis). Open squares, closed triangle, open circles, and closed squares correspond to the same symbols in (A) (closed circles correspond to the epidemic). Some approximated correlation lines were drawn using the “power approximation” in Excel file.

of virulent strains of the influenza virus. For instance, young recruits from all over Japan were clustered in unhygienic military campuses in order to be sent to the First World War frontlines (7); large numbers of young women from poor rural families were sent by dealers to the blooming spinning industries and forced to work under near-slavery conditions (9); rapidly soaring price of the staple food, rice (increase in price from 13.62 sen [0.01 yen]/kg in August 1916 to 38.70 sen/kg in August 1918) triggered the “rice riots” in 42 of the 47 prefectures, involving nearly 1 million people (10); and riots by poor farmers claiming their own farm lands occurred in 40 prefectures in the year 1921 alone (10). The Spanish flu has been documented to have been particularly rampant among recruits in military campuses and women workers in the spinning industries (7). Such populations could be associated with population B.

3-2. Asian flu

3-2-1. Time course of the epidemic

The document divides the epidemic into three waves (Fig. 6): the first wave was caused by influenza A1 and influenza B viruses and began toward the end of 1956 (open squares, Fig. 6A); the second wave peaked in June and July 1957 (closed triangles, Fig. 6A); and the third wave peaked in November–December 1957 (open circles, Fig. 6A). The epidemic period, as mentioned in the document, is indicated with a horizontal arrow.

3-2-2. Examining the applicability of the two-population hypothesis

Figure 6B shows the plot depicting the cumulative

number of patients and that of deaths. Plots including the epidemic waves (open and closed circles) appeared as straight lines with a slope k of ~ 2 , and could be reconstituted in a similar manner as the first or second wave of the Spanish flu, as per the “two-population” model. The population subjected to the rapid spread of the virus at a high death rate must have included school children and their families, because of documentation (3) that the entry of the Asian flu into Japan in 1957–1958 occurred at a time when the first baby boomers born in 1947–1949 were already of school age, and countless school outbreaks occurred. The documentation also observes that school excursions were responsible for the spread of the Asian flu throughout Japan. In addition, in those days in Japan, three-generation families comprised approximately 17% of households and approximately 55% of people aged >65 years lived with their children (<http://www.mhlw.go.jp/toukei/list/dl/20-21-01.pdf> [in Japanese]); therefore, elderly people could have contracted influenza from children.

The plots preceding (January 1956–August 1956) and succeeding (October 1958–December 1959) the epidemic were compatible with $k = 1$. When the total number of deaths was divided by the total number of patients, the case-fatality rates (%) were 11.2, 18.1, 17.9, 3.2, 12.54, 18.2, 2.9, 2.2, 0.8, 6.0, 5.2, and 2.8 in respective years from 1947 to 1960.

3-3. Hong Kong flu

Figure 7A shows the epidemic curve from January 1967 to December 1971. The epidemic roughly cor-

Fig. 7. Hong Kong flu epidemic (January 1967 to January–December 1971) and seasonal influenza epidemics before and after the epidemic. For source of data, see Fig. 6. (A) Time course of number of patients (plots connected by a solid line) and number of deaths (plots connected by a broken line) both reported monthly. The horizontal arrow indicates the duration of the epidemic assigned by the document (10). Vertical axis, number of patients and number of deaths; horizontal axis, number of months elapsed from January 1967 (open squares, January 1967–October 1967; triangles, November 1967–August 1968; open circles, October 1968–August 1969; open diamonds, September 1969–August 1970; crosses, October 1970–December 1971). (B) The log-log plots of cumulative number of deaths (in Y-axis) vs. cumulative number of patients (X-axis). Open squares, closed triangle, open triangles, open circles, open diamonds, and crosses correspond to the same symbols in panel A, and plots with open circles approximately correspond to the epidemic. Some approximated correlation lines were drawn using the “power approximation” in Excel file.

Fig. 8. Log-log plot of cumulative number of deaths (Y-axis) vs. cumulative number of patients (X-axis) for epidemics that occurred in 1955–1967. (A) Plots for epidemics before 1960–1961. See Fig. 6 for 1957–1958 between 1955 and 1960. (B) Plots for epidemics after 1960–1961. See Fig. 7 for 1967–1971 after 1967. Most approximated correlation lines were drawn by “power approximation” in Excel file.

responds to the plot (open circles); numbers of patients and death cases were not particularly high during the epidemic. All the plots of patients versus deaths were straight lines compatible with a slope of ~ 0.6 , with the exception of the epidemic period, when the slope k was ~ 1 (Fig. 7B). It should be recalled that in case of Asian flu, differently from Hong Kong flu, where the slope of seasonal influenza plots preceding and succeeding the

epidemic was ~ 1 .

3–4. Seasonal influenza

3–4–1. Epidemiological considerations

The slope k of seasonal influenza plots was ~ 1 in 1957–1958 and ~ 0.6 in 1967–1971, suggesting a transition in k from ~ 1 to ~ 0.6 between 1958 and 1967. Therefore, the slope k was estimated for the entire period 1955–1987; k was found to be ~ 1 until

Fig. 9. Transition of the age distribution of influenza patients and deaths in 1956–1967. The plots represent % of the total. Vertical axis: % of a given age group. Horizontal axis: 1, <5 yr; 2, 5–10 yr; 3, 10–20 yr; 4, 20–30 yr; 5, 30–40 yr; 6, 40–50 yr; 7, 50–60 yr; 8, 60–70 yr; 9, 70–80 yr; 10, 80–90 yr. Data of deaths were derived from Vital Statistics in Japan, “List of Statistical Surveys conducted by Ministry of Health, Labour and Welfare, Table: Deaths from each causes (detailed list) by sex and age; for all Japan. Data of patients were derived from Statistics of Communicable Disease and Food Poisoning Japan: “Statistics of Transmissible Diseases; Table: Number of cases for each disease (reportable) by sex and age-group.” For age distribution of population, see Fig. 13B and 13C. The age distribution was essentially the same for 1955 and 1965. All the population data used in this article are derived from <http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001007702> (in Japanese).

1960–1961, and then it changed to ~ 0.6 (Fig. 8A and 8B). The influenza reporting system remained unchanged during this period.

What caused this transition of k in 1960–1961? The age distribution of death cases shifted from the younger to older generation between 1960 and 1962 (Fig. 9B); the ratio between <10 year group and >70 year group was 51% vs. 1%, 28% vs. 31%, and 42% vs. 6% in 1956, 1958, and 1959, respectively (Fig. 9A); 50% vs. 31%, 27% vs. 45%, and 8% vs. 62% in 1960, 1961, and 1962, respectively (Fig. 9B); and 6% vs. 68%, 18% vs. 57%, and 17% vs. 55% in 1965, 1966, and 1967, respectively (Fig. 9C). Thus, the shift in age distribution of deaths toward the elderly population in 1960–1961 coincided with the transition of the slope k from 1 to ~ 0.6 . Interestingly, the 1950s–1960s corresponded to the period of accelerated economic growth of Japan. For example, the percentage of Japanese households having a refrigerator was <10% in 1960, 50% in 1965, and 90% in 1970; the corresponding percentages for an electric sweeper included <10% in 1960, 30% in 1965, and 70% in 1970. The annual GDP growth remained continuously high at 6.3%, 8.2%, 6.7%, 11.0%, 12.0%, 7.6%, 10.0%, 9.7%, 6.3%, 11.2%, 10.9%, 12.8%, 12.1%, 8.1%, 5.2%, and 9.0% in respective years from 1956 to 1971. The Olympics game was held in Tokyo in

1964, and the Osaka Japan World Exposition in 1970. The infant mortality rate (death within 12 months of birth) was 39.8 per 1,000 births in 1955, which reduced by half to 18.5 per 1,000 births in 1965 (<http://www8.cao.go.jp/youth/whitepaper/h22honpenhtml/html/zuhyo/zul106.html>, in Japanese). The nutritional status of Japanese population showed remarkable improvement during this time period; the average height of males and females at the age of 24 years was 160–165 cm and 155–160 cm, respectively, till 1970, but increased to 170 cm and 160 cm, respectively, in 1980 (<http://www2.ttcn.ne.jp/honkawa/2182.html>, in Japanese), indicating that nutritional status was greatly ameliorated toward the end of 1950s.

3–4–2. Examining the applicability of the two-population hypothesis

Plots of seasonal influenza with a slope k of ~ 0.6 were reconstituted using the two-population model for obtaining further insight into the epidemiology of seasonal influenza. Among the younger population, which is more prone to infection but less likely to succumb to influenza, the influenza virus is expected to spread faster but with lower death rate. On the other hand, among the less-active and frail elderly population, which has is less prone to infection but more likely to succumb to influenza, the influenza virus is expected

A-1	Observed	patients		deaths		d/p
		monthly	cumulative	monthly	cumulative	
	Jan-60	43	43	50	50	1.16
	Feb	712	755	60	110	0.08
	Mar	24440	25195	859	969	0.04
	Apr	91438	116633	2237	3206	0.02
	May	24440	141073	543	3749	0.02
	Jun	606	141679	96	3845	0.15
	July	397	141679	36	3881	0.09
	Aug	86	142162	24	3905	0.27

A-2	Model	population A		population B		A+B	
	Cumulative	patients	deaths	patients	deaths	patients	deaths
	t1	400	4	400	200	800	204
	t2	1600	16	800	400	2400	416
	t3	6400	64	1600	800	8000	864
	t4	25600	256	3200	1600	28800	1856
	t5	102400	1024	6400	3200	108800	4224
	t6	107200	1072	8000	4000	115200	5072
	t7	107600	1076	8800	4400	116400	5476

A-3	Model	population A		population B		population A+B		A+B
	Monthly	patients	deaths	patients	deaths	patients	deaths	
	t1	400	4	400	200	800	204	0.26
	t2-t1	1200	12	400	200	1600	212	0.13
	t3-t2	4800	48	800	400	5600	448	0.08
	t4-t3	19200	192	1600	800	20800	992	0.08
	t5-t4	76800	768	3200	1600	86400	2432	0.028
	t6-t5	4800	48	1600	800	6400	848	0.13
	t7-t6	400	4	800	400	1200	404	0.33

Fig. 10. Reconstitution of the seasonal influenza with slope k of ~ 0.6 . (A-1) Morbidity and mortality in the 1960 seasonal influenza (for closed circles in B). (A-2) (Model/cumulative): table used for log-log plot of cumulative number of patients vs. deaths in the reconstituted epidemics (for open circles in B). (A-3) (Model/monthly): table derived from the table in panel A-2; the figures are for the time span $t_{i+1}-t_i$ (for drawing the epidemic curve in Fig. 11B). (B) The log-log plot of cumulative numbers of the deaths (vertical axis) and the patients (horizontal axis). The reconstituted plots (open circles, 1960-model) overlap the observed plots (closed circles, January–August 1960). Approximated correlation lines were drawn by “power approximation” in Excel file.

to spread comparatively slowly and with higher death rate. In the model (Fig. 10), the former population was represented as population A and the latter population by population B for reconstitution of the epidemic (Fig. 10A-2 and 10A-3). The death rate D for the initial phase (time span t_1 to t_3) for populations A and B was set to 1% and 50%, respectively, and the multiplication rate M , to 4 and 2, respectively.

The epidemic progress is accompanied by decrease in virus-sensitive population and decline in the rate of new infection, corresponding to the time span t_6 to t_7 . The decline in transmission is expected to be more rapid in population A compared to population B, because population A is expected to become immune to the virus faster due to faster spread of the virus in this population. The figures in Fig. 10A-1, A-2, and A-3 are so adjusted without changing the values of D .

In Fig. 10, the reconstituted cumulative numbers of patients and deaths are tabulated in panel A-2 (Model/cumulative), and the reconstituted time-slot numbers in panel A-3 (Model/monthly), along with the observed data (A-1). The log-log plot of cumulative numbers of patients versus deaths obtained using the table in panel A-2 was almost identical to that of observed data (Fig. 10B).

The monthly plots depicting the number of patients and deaths (open and closed circles, respectively) during the seasonal influenza of 1960 are shown in Fig. 11A. The plot obtained using data from panel A-3 (Model/

monthly), which in turn were derived from panel A-2 (Model/cumulative), was qualitatively similar to that showing actual data (compare plots with open and closed circles in Fig. 11A and 11B; plots in triangles and squares in Fig. 11B correspond to the hypothetical subpopulations A and B).

Interestingly, in both the actual and reconstituted plots, the ratio of the number of deaths to the number of patients (d/p ratio) became low toward the peak of the epidemic, followed by an increase toward the end of the epidemic (compare plots with crosses in Fig. 11A and Fig. 11B). To examine if this is a general phenomenon, the number of patients, number of deaths, and d/p ratios from 1954 to 1967 were plotted in Fig. 12. The peaks of d/p ratio roughly coincided with the bottoms of the epidemic curve, thereby confirming the prediction of the model. Interestingly, in Spanish flu, such a trend with respect to d/p ratio was not observed (Fig. 1A and 1B).

4. Discussion

The present review revealed that the characteristics of an influenza epidemic are strongly dependent on the affected population. A slope k of > 1 occurred only in the case of Spanish flu and Asian flu. In both these cases, subpopulations among which the virus could spread faster and with higher mortality rates compared to the general population existed, including military recruits or

Fig. 11. The epidemic curve of the 1960 seasonal epidemic and that of a reconstituted seasonal epidemic. (A) Observed data. Vertical axis, number of patients (open circles), number of deaths (closed circles), and death/patient ratio (d/p ratio) in logarithm. Horizontal axis, numbers 1–8 correspond months from January to August 1960. (B) Epidemic curve reconstituted using A-3 (Model/monthly) in Fig. 10. Vertical axis, number of patients (open circles), number of deaths (closed circles), and death/patient ratio (d/p ratio) in logarithm. Horizontal axis, numbers 1–8 correspond time from t_1 – t_6 in Fig. 10A-3.

Fig. 12. Epidemic curve of influenza from January 1954 to December 1967. The plot of the patient number is in the top, that of deaths in the middle, and the deaths/patients rate (d/p) in the bottom. Peaks of the d/p rate approximately correspond to the bottoms of the patient and deaths numbers. For source of data, see Fig. 6.

spinning factory female workers who were clustered together under unhygienic conditions. In such conditions, the hosts are always within the reach of the virus, and the virus causing more severe symptoms is advantageous in its spread (8). In other words, in the absence of such conditions, the virulent strains are likely to be

outcompeted by their less-virulent variants (5). Therefore, application of drastic measures for making the spread of the virulent strains difficult, such as those applied by the World Health Organization during the 2009 H1N1 pandemic (1) and the recent H7N9 epidemic in China, will be extremely important for avoiding the

catastrophic consequences of influenza pandemic. The potential for virus evolution during an epidemic may have to be taken into account for pandemic management strategies.

With respect to seasonal influenza, the slope k shifted from ~ 1 to ~ 0.6 during 1960–1961, corresponding to a dramatic improvement in living conditions and shift in the age distribution of deaths due to influenza from the younger to older generation. Given that 24% of the total population of Japan at present (in 2013) is >65 years of age, it will be interesting to compare the characteristics of the current seasonal influenza with the ones that occurred in the 1970s. In the next 20 years (i.e., by 2033), 33% of the total Japanese population is expected to comprise individuals aged >65 years (http://www8.cao.go.jp/shoushi/kaigi/ouen/k_1/19html/sn-1-1-3.html [in Japanese]). Therefore, residential care homes for the elderly may have to be constructed on a large scale, and such facilities would prove ideal for the spread and evolution of the more-virulent strains of influenza virus. Infection control should therefore be seriously considered while planning such facilities where frail and elderly people are expected to be in close contact.

The age distribution of patients and fatalities in the different influenza epidemics were examined. Figure 13

shows the age distribution of influenza patients during the Spanish flu (panel A), Asian flu (panel B), and Hong Kong flu (panel C) epidemics.

The age distribution of patients, deaths, and the general population almost overlapped for the Spanish flu epidemic (Fig. 13A). The number of patients and death cases, as well as the population size for all the prefectures were filed side by side in columns using an Excel file, and correlation coefficient was obtained. Correlation between the numbers of patients and population sizes of prefectures was 0.96, that between numbers of deaths and population sizes was 0.82, and that between numbers of deaths and numbers of infection cases was 0.91. Thus, the Spanish flu virus appears to have infected and killed the Japanese population with equal efficiency irrespective of age and location. For the Asian flu, mortality was high in the age groups <5 (numbered 1 in the X-axis) and >60 years, while morbidity was high among the age group 5–30 years. For the Hong Kong flu, mortality, as in the case of the Asian flu, was high in the age groups <5 and >60 years, but shifted toward the older age group, reflecting the similar shift of seasonal influenza; morbidity was more limited to the age group 10–20 years than that in the case of the Asian flu.

Figure 14 shows the age distribution of the first 198

Fig. 13. Age distribution of patients, deaths, and population in Spanish flu, Asian flu, and Hong Kong flu. The plots represent % of the total. Horizontal axis: 1, <5 yr; 2, 5–10 yr; 3, 10–20 yr; 4, 20–30 yr; 5, 30–40 yr; 6, 40–50 yr; 7, 50–60 yr; 8, 60–70 yr; 9, 70–80 yr; 10, >80 yr. (A) Spanish flu. Data source is “Frequency of patients and deaths during the influenza epidemic seasons in 1919 and 1920 classified according to age and sex (based on information obtained from several cities, towns and villages)” in the document (2), and the age distribution of the population was also derived from the same document. (B) Asian flu in 1957–1958. (C) Hong Kong flu. The age distribution of influenza patients and deaths were obtained from Vital Statistics in Japan, “Deaths from causes (detailed list) by sex and month of occurrence (1968)” and data of patients from Statistics of Communicable Disease and Food Poisoning Japan: “Statistics of Transmissible Diseases; Table: Number of cases for each disease (reportable) by sex and age-group.” All the population data used in this article are derived from <http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001007702> (in Japanese).

Fig. 14. 2009 H1N1 influenza pandemic in Japan. (A) Age distribution (%) of 198 deaths due to the H1N1 pandemic 2009 from March 3, 2010 to August 15, 2010 in Japan. Data source is <http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/rireki/100331-03.html> (in Japanese). Horizontal and vertical axes, see figure legend of Fig. 9. Closed triangles represent the H1N1 pandemic influenza deaths, and open circles represent Japanese populations in 2005. (B) Age distribution (%) of the patients in 2005/6–2008/9 influenza seasons in Sapporo (13). Triangles represent age distribution of the 2009 H1N1 pandemic influenza patients and squares, diamonds, and crosses represent seasonal influenza in 2008/9, 2006/7, and 2005/6 seasons, respectively. Open circles represent age distribution in Sapporo (<http://www.city.sapporo.jp/toukei/tokeisyo/02populationl.html> [in Japanese]).

deaths of the 2009 H1N1 influenza pandemic in Japan (Fig. 14A). The age distribution of deaths in the 2009 H1N1 pandemic almost overlapped with that of the population, except in the case of the vulnerable age groups <10 and >70 years; this suggests that the influenza pandemic caused deaths almost evenly among different age groups, similar to the Spanish flu. Although highly speculative, the 2009 H1N1 influenza pandemic would likely have had the potential of causing devastating effects had it been introduced into Japan 100 years previously. Recent global mortality estimates suggest that the 2009 H1N1 virus had potentially high virulence (11). The case-fatality rate of the 2009 H1N1 epidemic was, however, as low as $\sim 0.002\%$ in Japan (the slope of the log-log plot was compatible with ~ 1 and intersected the X-axis at approximately 50,000) (12). Such a low value of the calculated case-fatality rate, however, is attributable to the heightened scare of the epidemic, which resulted in increased visits to clinics. The peak age distribution of patients was 10–20 years in the 2009 H1N1 pandemic (Fig. 14B), while it was 5–10 years for the seasonal influenza before and after the 2009 H1N1 epidemic.

Acknowledgments The author thanks Dr. K. Nakajima, Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare, for information of the data sources and valuable discussions and Dr. M. Noji, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, for information of the data sources.

Conflict of interest None to declare.

REFERENCES

- Yoshikura H. On case-fatality rate: review and hypothesis. *Jpn J Infect Dis.* 2012;65:279–88.
- Department of Hygiene. Epidemic influenza-record of the grand epidemic of “Spanish Flu.” Toyo-Bunko. Tokyo: Heibon-sha; 2008. Japanese.
- Japan Public Health Association. Asian flu-record of A2 influenza epidemic (1957–1958). Tokyo: Japan Public Health Association; 1960. Japanese.
- Japan Public Health Association. Hong Kong flu-record of the epidemic. Tokyo: Japan Public Health Association; 1971. Japanese.
- Yoshikura H. Two parameters characterizing 2009 H1N1 swine influenza epidemic in different countries/regions of the world. *Jpn J Infect Dis.* 2009;62:411–2.
- Yoshikura H. Two-population model accounting for the different patterns observed in the log-log plot of the cumulative numbers of those infected and killed in the early phase of the 2009 H1N1 pandemic in contrast to the one-population model accounting for the 1918–1919 pandemic in San Francisco. *Jpn J Infect Dis.* 2009; 62:482–4.
- Hayami A. Spanish flu that devastated Japan. Tokyo: Fujiwara Shoten; 2009. Japanese.
- Ewald PW. Evolution of infectious disease. Oxford: Oxford University Press; 1994.
- Hosoi K. Sad history of spinning industry women workers. Iwanami-Bunko. Tokyo: Iwanami Shoten; 1954. Japanese.
- Toriumi Y. Read again Yamakawa modern history of Japan. Tokyo: Yamakawa Shuppan-Sha; 2013. Japanese.
- Simonsen L, Spreeuwenberg P, Lustig R, et al. Global mortality estimates for the 2009 influenza pandemic from GLaMOR project: a model study. *PLOS Med.* 2013;10:e1001558.
- Yoshikura H. Common features of 2009 H1N1 influenza pandemic in different parts of the world revealed by log-log plot of the cumulative numbers of infected and deceased cases. *Jpn J Infect Dis.* 2010;63:148–9.
- Ogiya Y, Mizushima Y, Takahashi H, et al. Age and sex distribution of influenza patients reported from influenza sentinel points in Sapporo City—comparison with the seasonal influenza. *Ann Sapporo Public Health Inst.* 2010;37:39–45. Japanese.