

# Epidemiology of a primary pneumonic plague in Kantoshu, Manchuria, from 1910 to 1911: statistical analysis of individual records collected by the Japanese Empire

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Background	Among the potential uses of <i>Yersinia pestis</i> , intentional release of its aerosolized form, causing person-to-person transmission, is thought to be the most threatening. With the current rarity of pneumonic plague epidemics, our epidemiological knowledge remains insufficient for detailed characterization of effective control measures.
Methods	Temporal patterns and key biological parameters of a pneumonic plague epidemic in Manchuria from 1910 to 1911 were analysed based on historical records collected by Kanto Totokufu, the administration of the Japanese Empire in Manchuria at that time. The serial intervals were fitted to gamma distribution using the maximum likelihood method, and time-delay distributions from onset-to-admission, admission-to-death, and onset-to-death were investigated.
Results	Whereas a total of 228 cases were diagnosed with pneumonic plague in areas under direct control of the Japanese Empire, 4781 cases were also recorded in surrounding areas. Although the epidemic grew exponentially in the early phase, the average doubling time steadily increased reflecting successful control efforts. The estimated mean serial interval (and standard deviation) was 5.7 (3.6) days. All cases with known dates of onset were admitted to hospital within 4 days after onset, and the mean time from onset to admission was 1.1 (0.4) days.
Conclusions	The increase in doubling time demonstrates the efficient and rapid counter-measures employed. Since the short interval from onset to death implies the importance of rapid responses, the challenge in confronting a future bioterrorist attack is to implement rapid and appropriate integration of control measures both at the individual and community level to prevent further transmissions as well as lower case fatality.
Keywords	Epidemiology, pneumonic plague, epidemics, statistical distributions, confidence intervals, historical events

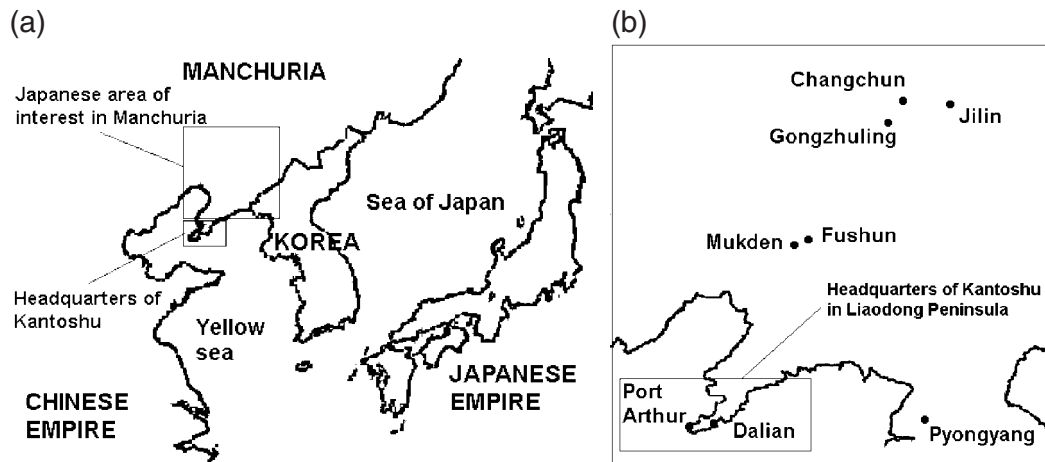
Although the annual incidence of plague has gradually decreased,<sup>1</sup> there is a plausible worldwide threat of bioterrorist

attack using the causative agent *Yersinia pestis*.<sup>2,3</sup> The Centers for Disease Control and Prevention (CDC) classified this agent as category A owing to its biological as well as epidemiological characteristics and potential impact.<sup>4</sup> Among its potential uses, intentional release of aerosolized *Y. pestis*, causing person-to-person transmission of primary pneumonic plague, is thought to be the most threatening. The proportion of pneumonic plague-associated case fatalities without appropriate treatment within 24 h after onset is thought to be ~100%.<sup>5</sup> There are still no specific methods of primary prevention such

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**Figure 1** Political map of Far East Asia from 1910 to 1911. (a) Political areas in Far East Asia from 1910 to 1911. Both Japanese and Russian armies evacuated Manchuria after the Treaty of Portsmouth in 1905, but the Japanese Empire remained in Liaodong Peninsula, which contains Dalian and Port Arthur, under control of the headquarters of the Empire, Kantoshu (small boxed area). The power of Kantoshu progressed northward (large boxed area) owing to penetration of the Japanese Empire with the building of the Manchurian Railway; this became the preceding political zone of Manchukuo after 1931. After falling under the Japanese Protectorate between 1905 and 1910, Korea was annexed as a part of the Japanese Empire from 1910 to 1945. (b) Enlarged map of Kantoshu and areas illegally penetrated up to 1910–11. The Manchurian Railway connected Changchun and Dalian. Only Liaodong Peninsula was completely under the direct control of Kantoshu. Other northern cities, including Mukden, Fushun, Changchun, and Gongzhuling, were partly occupied by the Japanese Empire (around train stations only); surrounding areas remained under political control of the Chinese Empire. The map was drawn by the author with reference to a historical map<sup>30</sup>

as vaccine,<sup>6</sup> and the appearance of multi-drug-resistant strains implies potential difficulties of treatment in the case of future attacks.<sup>7</sup> Since real-time observations of large-scale primary pneumonic plague epidemics are now extremely rare, historical records can assist in determining key information. Reviewing historical epidemic records has been effective in the search for potential control strategies,<sup>8,9</sup> and accumulation of different epidemic records has helped obtain estimates of important biological and epidemiological parameters.<sup>10,11</sup> Nevertheless, owing to the scarcity of reports and relatively small size of each epidemic to date, our knowledge on the epidemiology of pneumonic plague is still insufficient for detailed characterization of effective control measures, and, hence, further investigation is required. To date, the biggest epidemic of pneumonic plague to be documented with bacteriological confirmation was that in Manchuria from 1910 to 1911.<sup>12</sup> Whereas the statistical records of this epidemic in the report of the International Plague Conference held in Mukden, Manchuria, 1911, were fragmentarily collected from different locations (i.e. from several plague hospitals) owing to the large number of deaths and rapidity of spread beyond the capacity of the health authorities,<sup>13</sup> detailed documentation was also performed within the political zone of the Japanese Empire in Manchuria at that time. In the present study, total and individual case records are analysed based on the report of Kanto Totokufu,<sup>14</sup> the administration section in charge of the political areas of the Japanese Empire in Manchuria, with particular emphasis on key distributions and parameter estimations over time.

## Materials and methods

### Brief history of Kantoshu and Kanto Totokufu

After the end of the Russo-Japanese War with the signing of the Treaty of Portsmouth in 1905, several parts of Manchuria,

such as Dalian, came under direct political control of Kantoshu, an annex of the Japanese Empire.<sup>15</sup> Although Kantoshu represented the political area of the Japanese Empire in Liaodong Peninsula, its overall power progressed northward through construction of the South Manchurian Railway and subsequent penetration of the Empire (Figure 1a). In this enlarged political area (i.e. the headquarters of Kantoshu in Liaodong Peninsula and the areas around train stations in several cities in Manchuria; see Figure 1b), Kanto Totokufu, which was established in 1906, was placed in charge of controlling administration, including public health practices. Remaining areas were under the political control of the Chinese Empire. At the time of the pneumonic plague epidemic in Manchuria, Kanto Totokufu organized a temporary quarantine section. Task force members were also given the responsibility of performing investigations and summarizing the statistical records of the epidemic in and around areas under direct control of the Japanese Empire.<sup>14</sup>

### Data source: description of the historical observation

In 1910, owing to the uncontrollability of the plague epidemic in Chinese controlled areas, Kanto Totokufu urgently requested medical professionals and their assistants from the Japanese Islands. Organizations receiving these requests included the Japanese Ministry of the Interior, the National Institute of Communicable Diseases (presently The Institute of Medical Science, The University of Tokyo), and Osaka and Hyogo prefectures. Since Kanto Totokufu viewed the epidemic as a serious political and economic threat,<sup>16</sup> an extraordinary number of professionals were assigned to assist in the disease control tasks. A total of 2182 police guards were engaged in contact tracing and quarantine, while 7339 others worked for the temporary quarantine section.

The total number of documented pneumonic plague cases was 5009, including those from areas surrounding Kantoshu. Based on efforts within areas under direct political control of Kantoshu,<sup>14</sup> individual data were obtained for 228 cases, enabling detailed epidemiological investigations. Individual information included name, sex, age, diagnostic methods, source of infection, and dates of onset, discovery, hospital admission, and death. The 228 individual records covered observations made after notification of the index case on December 31, 1910 until the end of the epidemic on April 17, 1911. The remaining 4781 cases were diagnosed in surrounding areas and provided the date of notification only. Since the epidemic became remarkable in other areas of Manchuria from early October 1910,<sup>17</sup> public health measures such as contact tracing, quarantine, and isolation were extensively performed at the time of record collection. At this time, there was no specific effective treatment for pneumonic plague.<sup>18</sup>

### Statistical analysis

As descriptive information, temporal distributions of pneumonic plague cases in and around areas under direct control of Kantoshu were obtained. Spatial information was obtained only within directly controlled areas, and reliable demographic data were unavailable. Based on the total daily number of reported cases, doubling time,  $T$ , was given by:

$$T = \frac{t_k - t_0}{\log_2 \left( \frac{N_k}{N_0} \right)} \quad (1)$$

where  $N_k$  and  $N_0$  are the cumulative number of cases at times  $t_k$  and  $t_0$ , respectively. Since 88 of the 228 records included a definitive description of the potential source of infection based on room sharing in a hospital or at home, the serial interval, the time interval between infection of one person and infection of others by this individual (or the time from symptom onset in the index case to symptom onset in a secondary case),<sup>19</sup> was estimated from these data. The interval was fitted to a gamma distribution using the maximum likelihood method. The Cramer–Smirnov–von Mises test was employed to assess the goodness-of-fit.<sup>20</sup> Time-delay distributions (from onset-to-admission, admission-to-death, and onset-to-death) were also investigated. Since these distributions did not reasonably fit standard statistical distributions, estimates were obtained as sample means and standard deviation (SD), not assuming specific distributions. To estimate the parameters of the above three time-delay distributions, only those cases for which required information was available were used, ignoring incomplete observations. The statistical data were analysed using the statistical software JMP IN version 5.1 (SAS Institute Inc., Cary, NC).

## Results

### Descriptive data and temporal distributions

Among a total of 5009 recorded plague cases, 228 were diagnosed as having pneumonic plague in areas under direct control of Kantoshu. Figures 2a and b show the temporal distributions in surrounding and directly controlled areas, respectively. These results are based on the dates of notification, and, hence, include delays in discovery of death, diagnosis, and reporting. Notifications peaked in late

January 1911 in directly controlled areas and in mid-February 1911 in surrounding areas, while the records of other Chinese controlled areas peaked in late November and December, 1910.<sup>13</sup> The cumulative number of cases in both areas on a logarithmic scale is given in Figure 2c. The epidemic showed an exponential increase in the early phase. The average doubling time for the total number of reported cases is given in Figure 2d. After a drop in early January, the doubling time continued to increase over time. Supplementary data 1 shows the number of cases with time used to create these temporal distributions (Supplementary data available at *IJE* online).

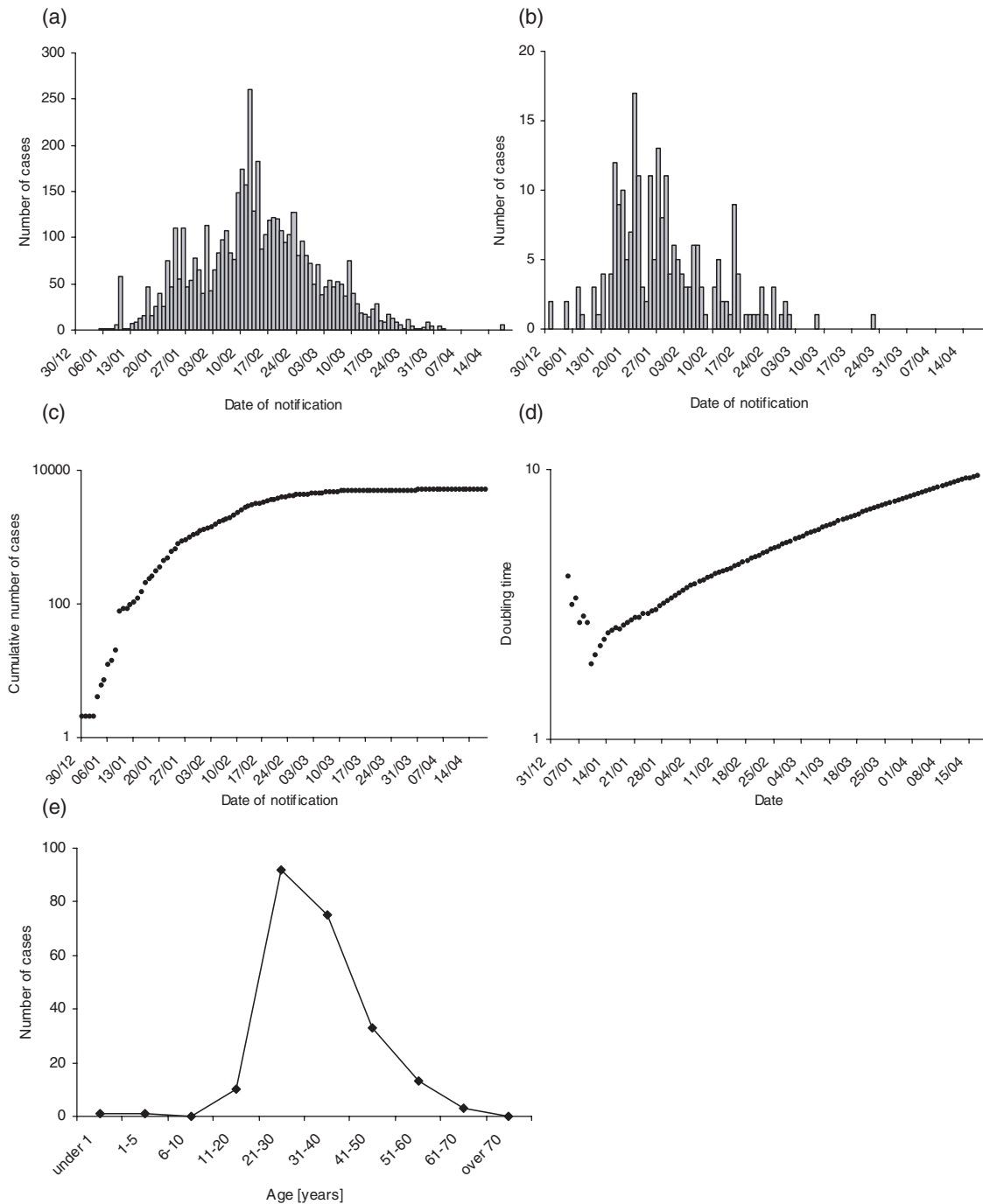
Detailed individual records were obtained for all 228 cases diagnosed in the directly controlled areas. The mean age and SD of these cases were 33.2 and 10.6 years, respectively; a crude age distribution is shown in Figure 2e. The majority of cases consisted of adults aged between 21 and 50 years ( $n = 200$ , 87.7%). Only two cases were female (0.9%). In directly controlled areas (Figure 1b), the majority of cases were diagnosed in Changchun ( $n = 105$ , 46.1%) and Dalian ( $n = 65$ , 28.5%); other places included Fushun ( $n = 18$ , 7.9%), Mukden (presently Shenyang;  $n = 13$ , 5.7%), and Gongzhuling ( $n = 12$ , 5.3%).

Diagnosis was made mainly by sputum examination under a microscope or sputum culture of *Y. pestis* (Table 1). Numbers diagnosed using each method in Table 1 denote successful confirmation with shown diagnostic tests. Nearly 40% of cases were confirmed by a combination of these two methods. However, diagnoses of 51 cases (23.1%) were confirmed by pathological examination after death, and, of these, 66.7% were further confirmed using bacterial culture of samples. Only 16 cases (7.2%) were diagnosed by means of clinical examinations alone. The records suggest that clinical diagnoses were almost all based on signs of respiratory failure with bloody sputum.

### Distributions of the serial interval and time delays

The maximum likelihood estimates of the mean serial interval and SD were 5.7 [95% confidence interval (95% CI) 4.9–6.4] and 3.6 days, respectively. Therefore, the shape and scale parameters of the gamma distribution were 2.5 (95% CI 1.9–3.3) and 2.2 (95% CI 1.7–3.1), respectively. As a visual comparison, the Kaplan–Meier survival curve together with the parametric cumulative survival probability is given in Figure 3a. The mean [and corresponding standard error (SE)] in the non-parametric method was also estimated as 5.7 (0.4) days. Cramer–von Mises goodness-of-fit test revealed no significant deviation between the observed and expected distributions ( $W^2 = 0.17$ ,  $P = 0.25$ ). Supplementary data 2 includes the serial intervals for the 88 investigated cases (Supplementary data available at *IJE* online).

Figures 3b–d show the frequencies of time from onset-to-death, onset-to-admission, and admission-to-death on a discrete time scale. The estimated mean and SD for these three time periods were: 2.3 and 1.7 days; 1.1 and 0.4 days; and 0.9 and 1.1 days, respectively. In each case, there was no significant association with age ( $P = 0.55$ , 0.13, and 0.77, respectively). The main reasons for exclusion from Figures 3b–d were cases with unknown dates of onset ( $n = 62$ , 27.2%), those not admitted to hospital and who died soon or suddenly after discovery ( $n = 85$ , 37.3%), and those found dead ( $n = 4$ , 1.8%). All confirmed cases investigated here resulted in death.



**Figure 2** Epidemiological description of the primary pneumonic plague epidemic in and around Kantoshu, Manchuria, from 1910 to 1911. (a) Temporal distribution of plague notifications in surrounding areas ( $n = 4781$ ) and (b) areas under direct control of Kantoshu ( $n = 228$ ). (c) Logarithmic temporal distribution of the cumulative number of cases in and around the directly controlled areas ( $n = 5009$ ). (d) Doubling time of the primary pneumonic plague epidemic in and around the directly controlled areas with time ( $n = 5009$ ). (e) Age distribution of cases in directly controlled areas ( $n = 228$ )

## Discussion

Epidemic records of a pneumonic plague epidemic in Manchuria from 1910 to 1911 were analysed based on 5009 cases included in the report by Kanto Totokufu, the administration in charge of the political areas of the Japanese Empire in Manchuria at the time. Several key statistical distributions were obtained for 228 individual pneumonic plague cases

diagnosed in areas under direct control. All investigated cases resulted in death. As in recent rigorous studies on severe acute respiratory syndrome (SARS),<sup>21,22</sup> obtained distributions statistically reflect the biological and epidemiological characteristics of the course of a disease and epidemic. For example, in the examined epidemic, individuals, excluding those found after or close to death, were efficiently admitted to hospitals within 4 days

after onset. As has been discussed previously,<sup>23</sup> this reflects the severity of pneumonic plague, which leads to death within a short time period without treatment, or extent of the control measures.

The epidemic period investigated in this study saw extensive interventions implemented almost from when the collection of official records was started.<sup>14</sup> Since there was no specific

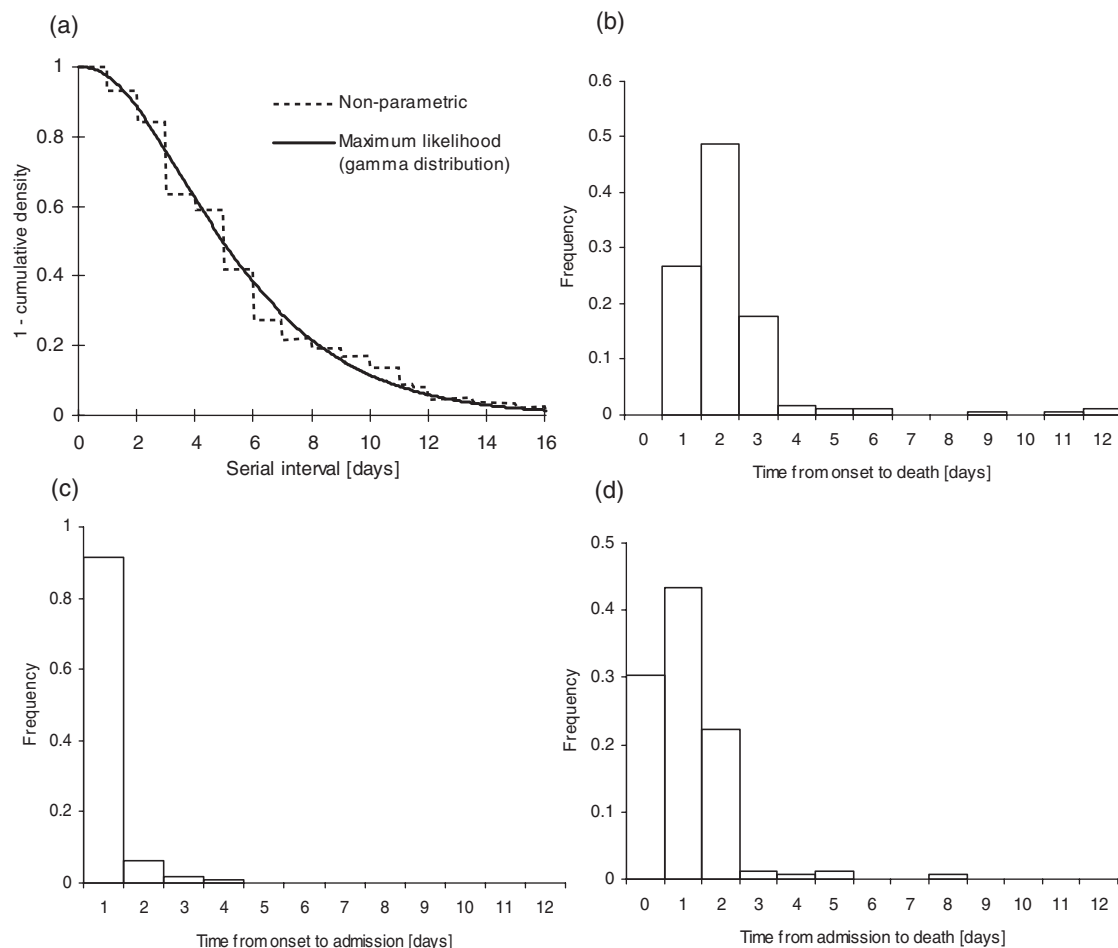
**Table 1** Diagnostic methods used to confirm diagnoses of primary pneumonic plague in Kantoshu, Manchuria, from 1910 to 1911 ( $n = 221$ )

Diagnostic method	<i>n</i>	Percentage
Sputum culture	161	72.9
Microscopic examination of sputum	110	49.8
Pathological diagnosis <sup>a</sup>	51	23.1
Blood culture	46	20.8
Clinical diagnosis only	16	7.2
Microscopy and culture of sputum <sup>b</sup>	86	38.9
Anatomy and culture of samples <sup>b</sup>	34	15.4

<sup>a</sup> Pathological diagnosis was made by autopsy and, in part, histopathological examination.

<sup>b</sup> Combined methods.

treatment for pneumonic plague at this time, most of the efforts by Kanto Totokufu were devoted to prevention both at the individual and community level. At the individual level, the use of a gauze mask was recommended almost as obligatory practice not only for those participating in public health and medical practices (e.g. sanitary officers and hospital assistants) but also the general population.<sup>24</sup> Through household rounds, the notifications of infected and deceased persons were strictly supervised, and at the same time, an attempt was made to educate the public about the mode of transmission, disinfection methods, and rodent traps (partly based on knowledge of bubonic plague control).<sup>14</sup> At the population level, it is documented that public health interventions included not only quarantine of potentially infected cases and isolation measures but also screening and identification of possible contacts in order to find infected individuals, i.e. contact tracing.<sup>15,25,26</sup> Because the number of hospital beds appeared to be too few to admit all cases, Kanto Totokufu constructed temporary camps for isolation purposes only, whereby contact was kept under strict observation.<sup>14</sup> Since pneumonic plague is known to have spread spatially as a result of construction of the Manchurian Railway,<sup>27</sup> clinical examinations and quarantines



**Figure 3** Frequency distributions of key epidemiological determinants of primary pneumonic plague based on the records of Kanto Totokufu, Manchuria, from 1910 to 1911. (a) Non-parametric (broken line) and maximum likelihood gamma probabilities (solid line) of the serial interval given as the cumulative survival probability ( $n = 88$ ). (b) Onset-to-death distribution ( $n = 166$ ). (c) Onset-to-admission distribution ( $n = 126$ ). (d) Admission-to-death distribution ( $n = 143$ )



were also performed in areas surrounding each train station on the line.<sup>28</sup> Moreover, traffic restrictions were implemented to limit movement of infectious individuals into highly populated areas; in particular, complete road blockage was performed in rural locations where no trained sanitary officers were placed.<sup>14,24</sup> As a result, whereas an exponential increase was observed in the early stages of the epidemic, the doubling time slowly but steadily increased over time due to lowered transmission rates and the effectiveness of the control efforts.<sup>29</sup> This increase reflects eventual control of the epidemic in investigated areas.

The important implications of the present findings are the requirement for rapid responses during potential future epidemics. Although the investigated epidemic, which lasted for more than 3 months, differs from those at present where effective public health interventions include quick release of information through mass media, the historical records suggest the potential for disaster even with considerable preventive measures both at the individual and community level. Whereas the investigated epidemic eventually declined to extinction as a result of concerted efforts, one of the biggest current concerns over pneumonic plague is the extremely high risk of death

following the short symptomatic period. Even though there are now several specific treatment methods, even a slight time lag from onset to admission could result in death. Therefore, the challenge in confronting a future bioterrorist attack is the implementation of extremely rapid and appropriate integration of individual and community interventions. Although primary pneumonic plague is highly fatal and its aetiological agent *Y. pestis* is readily available, epidemiological studies of this disease as well as investigations of intervention strategies remain rather limited compared with those for smallpox. In this context, biological and epidemiological research on pneumonic plague should be strengthened in the future.

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### KEY MESSAGES

- Whereas an exponential increase was observed in the early stages, the doubling time steadily increased over time reflecting effective control measures.
- Pneumonic plague cases, excluding those found after or close to death, were admitted to hospitals within 4 days after onset.
- The challenge in confronting a future bioterrorist attack is rapid and appropriate integration of control measures both at the individual and community level to prevent further transmissions as well as lower case fatality.

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Copy of poster published by the Ministry of Interior, Japanese Empire, from the influenza epidemic in 1918.

The top figure promotes the use of masks inside the train. Because the use of masks has been known to be effective to prevent droplet infections during the Manchurian plague outbreak, and because the train has been recognized as the most dangerous setting through the experience of Manchurian plague outbreak, the government suggested all individuals should wear the mask during the influenza epidemic. The bottom figure promotes gargling for those returning from outside. Whereas the effectiveness of gargling is still questionable even at present, the government encouraged everyone to wash their tonsils everytime after walking outside. The Japanese words in the middle are almost equivalent to the slogan. This says 'Wear the mask within the train and crowds!' and 'Don't forget gargling after coming back from outside!'. The title at the bottom is 'Mask and gargling'.