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Assessment of Intervention Measures for the 2003 SARS Epidemic in Taiwan by Use of a Back-Projection Method

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OBJECTIVES. To reconstruct the infection curve for the 2003 severe acute respiratory syndrome (SARS) epidemic in Taiwan and to ascertain the temporal changes in the daily number of infections that occurred during the course of the outbreak.

METHOD. Back-projection method.

RESULTS. The peaks of the epidemic correspond well with the occurrence of major infection clusters in the hospitals. The overall downward trend of the infection curve after early May corresponds well to the date (May 10) when changes in the review and classification procedure were implemented by the SARS Prevention and Extermination Committee.

CONCLUSION. The major infection control measures taken by the Taiwanese government over the course of the SARS epidemic, particularly those regarding infection control in hospitals, played a crucial role in containing the outbreak.

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The severe acute respiratory syndrome (SARS) epidemic of 2003 presented one of the most serious global health threats since the emergence of human immunodeficiency virus (HIV). Uncertainty about clinical and epidemiological aspects of the novel SARS coronavirus made it difficult to determine appropriate public health interventions to contain the epidemic during the course of the outbreak.¹⁻³ Despite the lack of a quantitative method to justify the effectiveness of intervention measures at the population level, monitoring changes in the daily number of infections over the course of the epidemic may provide some insight into the immediate impact and effectiveness of these measures. An infection curve is a plot of the daily counts of new infections over the course of the epidemic. The infection curve for an epidemic would be a useful and convenient tool for evaluating the effectiveness of intervention measures.⁴ However, the daily number of infections is unobservable. The available information on the daily number of reported cases, with an unknown individual disease incubation period, is not sensitive enough to reflect the spread of the epidemic over the course of the outbreak. The immediate effect of the intervention measures is therefore difficult to ascertain. Nevertheless, prompt and decisive action is needed in efforts to contain newly emerging epidemics, such as the potential threat of pandemic influenza. Hence, a procedure for the construction of an infection curve using statistical methods is highly desirable.

In this study, we adopted a back-projection method similar to that used by Chau and Yip⁴ to examine the SARS epidemic in Taiwan. The back-projection method has been widely used in modeling the spread of HIV infection and acquired immune deficiency syndrome.⁵⁻⁷ The clinical course of SARS progresses from infection, through incubation, to onset of symptoms, so the back-projection technique can be readily used in this context. With updated SARS case data, we were able to reconstruct the infection curve for the SARS outbreak in Taiwan and show that the fluctuations on the infection curve fit well with the major events on the time line of that outbreak. A discussion of the public health implications of our results is also provided here.

METHODS

Data

According to the Taiwan Center for Disease Control (TCDC)⁸ and the World Health Organization (WHO),⁹ 346 patients in Taiwan were officially confirmed as having SARS. Among them, there were 37 deaths directly caused by SARS (ie, the cause of death was recorded as SARS) and 36 SARS-related deaths (ie, the cause of death was not directly attributed to SARS). However, in a follow-up study done in collaboration with the TCDC to track previously unconfirmed cases, a total of 134 additional SARS coronavirus antibody-positive pa-

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tients were found to have laboratory-confirmed cases of SARS, 12 of whom died.¹⁰ Consequently, the total number of confirmed SARS cases in Taiwan by the end of December 2004 was 480, which is different from the figure cited in earlier published reports on SARS in Taiwan.¹¹⁻¹⁵ The definition of a SARS case used in Taiwan is the same as that used by the WHO.^{14,16} These 480 cases with onset of symptoms occurring between February 25, 2003, and June 25, 2003, were used in the present study. To our knowledge, this is the first back-projection study of the Taiwan SARS outbreak that makes use of the more comprehensive data set of laboratory-confirmed SARS cases.

Statistical Analysis

We proposed to use the back-projection method to estimate the daily counts of newly infected people, or the mean daily number of new infections. The back-projection method assumes a known distribution for the incubation period on the basis of data from other studies. The details of the model employed, including the model assumptions and model parameters, are given in Appendix A. For our study, we assumed that the incubation period followed a gamma distribution. The details pertaining to the choice of gamma distribution can be found in Appendix B.

It has been shown that age was an important factor in the SARS case-fatality rate.²⁰ Similarly, it was of interest here to examine how age was related to infection intensity. The estimates of the daily number of infections would certainly be more accurate and precise, given the additional information, if age was an important factor.⁵ The Kruskal-Wallis test was employed to test for the homogeneity of incubation distributions among 3 age groups: 0-14 years, 15-59 years, and 60 years and older. The effect of age was not significant; the null hypothesis of homogeneity was not rejected at the 5% significance level ($P = .36$). Therefore, no age-adjusted expectation-maximization-smoothing algorithm⁴ (EMS; see Appendix B) was used to estimate the infection curve of the Taiwan SARS epidemic.

RESULTS

Figure 1 gives the estimated daily number of SARS infections, λ_t , from February 18 to June 17, 2003. The point-wise 95% confidence interval for λ_t was constructed for each time point t by using a bootstrapping method.⁶ A chronological summary of intervention measures taken in Taiwan²¹ is also given in Figure 1.

The major peaks of the estimated λ_t values at the height of the outbreak in Taiwan corresponded well with the occurrences of major SARS-related events in Taiwan hospitals. The first peak, identified as occurring on approximately April 17, corresponded to the infection clusters at Hoping Hospital and Jenchi Hospital that resulted in the escalation of the outbreak in Taiwan and, subsequently, the shutdown of Hoping Hospital on April 24 and the shutdown of Jenchi Hos-

pital 2 days later. The second peak, identified as occurring on approximately April 25, corresponded to the infection clusters at the National Taiwan University Hospital emergency department (which was shut down on May 12), McKay Hospital, and Chung-Hsing Hospital in Taipei.^{14,22} The third and last peak, identified as occurring on approximately May 5, corresponded to the nosocomial infection cluster at Kaohsiung Chang Gung Memorial Hospital in the southern city of Kaohsiung. A smaller peak occurring on approximately May 15 corresponded to the infection cluster at Kuandu Hospital in Taipei.

During the height of the outbreak (from mid-April to early May), the trough in estimated λ_t values occurring on approximately April 21 corresponded to an infection cluster at Hoping Hospital being reported to the health authorities on April 21 and 22, resulting in a heightened alertness for hospital infection control personnel that lessened the spread of nosocomial infections at Hoping Hospital. The second trough, occurring on approximately April 30, corresponded well to the implementation of level B quarantine policy on April 28; this marked the start of large-scale border control and home quarantine, which turned out to be the major turning point for ending the outbreak in Taiwan.²³ Furthermore, the overall downward trend of the infection curve after early May corresponded well to a change in review and classification procedures implemented by the cabinet-level SARS Prevention and Extrication Committee in Taiwan on May 10 to expedite the review and reclassification of suspected SARS cases in an effort to quickly identify and isolate the patients who truly had SARS.²¹ April 28 was determined to be an important date for significantly expediting quick identification of suspected cases (thereby decreasing the time between onset and diagnosis), and May 10 was an important date for swiftly classifying probable cases (thereby decreasing the time between diagnosis and reclassification).¹⁰

DISCUSSION

The estimated daily number of infections during the course of an epidemic is a good indicator of the infection intensity. The immediate benefit of certain effective intervention measures is easily seen because of their influence on reducing the daily number of infections. With the convolution of the incubation period, the time at which a patient is infected is unobservable. Hence, it is desirable to use statistical methods to reconstruct the infection curve that allow for the evaluation of the effectiveness of intervention measures. The back-projection method, which is a very useful tool in modeling epidemics, can be readily used in this context.

The use of the back-projection method, relying on the aggregate observed daily number of patients with confirmed SARS, to construct the infection curve has advantages over tracing the patients' contact history, as done by Karlberg et al.²⁴ The case-study method²⁴ is very useful in understanding the epidemic. However, it is not efficient and may be very

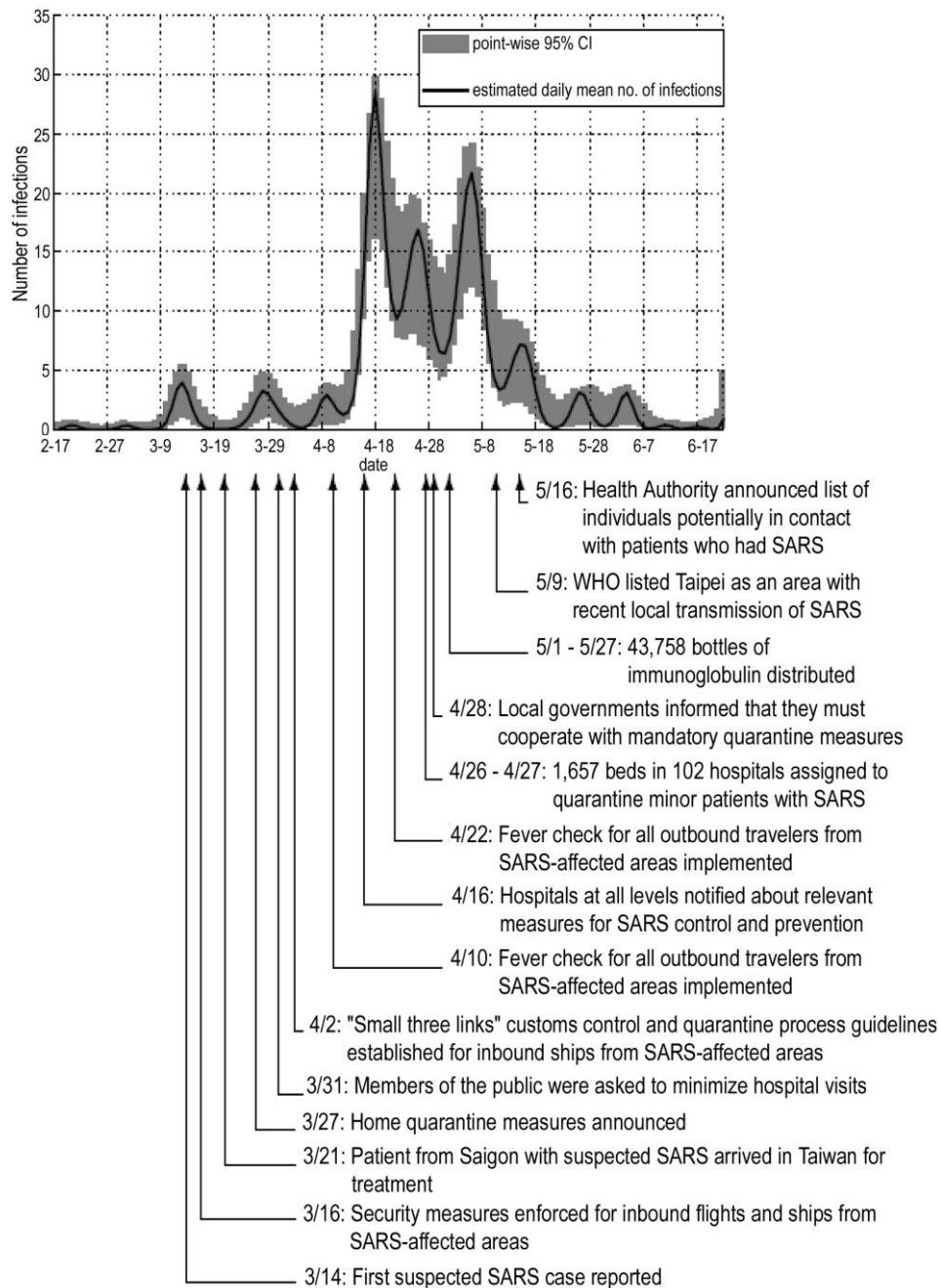


FIGURE. Time line showing estimated daily mean number of severe acute respiratory syndrome (SARS) cases (and point-wise 95% confidence intervals [CIs]) during the 2003 outbreak in Taiwan and major infection control interventions. WHO, World Health Organization.²¹

time consuming, because a detailed contact history for each individual is needed. Moreover, such information is usually unavailable and/or unreliable, especially during the course of the epidemic, and the infection curve estimated by the case-study method is subject to individual fluctuations. The estimated infection curve obtained from the back-projection method smooths out these fluctuations so that waves of in-

fection can be clearly identified. Chau and Yip⁴ used the back-projection method to analyze the 2003 SARS outbreak in Hong Kong. They managed to show that 4 waves of infection had occurred over the course of that outbreak. It is interesting to note that 3 of the 4 waves (ie, all except the outbreak at Amoy Garden)⁴ originated in hospitals.

Other similar studies on the evaluation of intervention

measures used during SARS outbreaks can be found in Hsieh et al.²³ and Pang et al.²⁵ Hsieh et al.²³ applied the Richards model²⁶ to the daily cumulative number of cases during the Taiwan SARS outbreak, and they estimated that April 28 was the turning point of the outbreak: on this date, the growth rate of the cumulative number of cases attained its maximum level, decreasing gradually thereafter. However, this method does not provide information on each major and minor wave of the epidemic. Pang et al.²⁵ utilized the time lag between onset of illness and hospitalization during the Beijing SARS epidemic. This method is very simple and can be computed quite easily by hand. However, the evaluation of control measures with this method was further complicated by the time lag of at least 1 incubation period between implementation of the measure and the time that the intervention took effect.

The Taiwan SARS outbreak displayed a pattern very similar to that of the Hong Kong outbreak. Each major peak of the outbreak corresponds to infection clusters in hospitals. If the infection control measures in affected hospitals were more effective, it is likely that the epidemic could be contained within the hospital compounds and would not be able to spread as readily to other patients, hospital staff, and visitors in the hospitals, and, subsequently, would not spread as readily to the community. There are a number of issues that need to be critically addressed in the control and prevention of SARS or any emerging infectious disease in hospitals. The availability of isolated wards to prevent cross-infection between patients with and patients without SARS, as well as the adequate supply of protective equipment and medical items, all play important parts in containing the epidemic. Nevertheless, the professionalism exhibited by the medical and healthcare staff during the outbreak, in terms of their dedication, sacrifice, and medical knowledge and training, is also a crucial factor in combating the disease.

Although infection intensity did not show significant age dependence, the SARS fatality rate was found to be age dependent.²⁰ It is also important to advise people to seek appropriate medical assistance immediately after the onset of possible symptoms. However, hospitalization might actually increase the risk of infection as a result of an insufficient number of isolation wards in hospitals and overstressed medical staff dealing with an influx of persons with suspected (but not genuine) cases. Consequently, in the case of a newly emerging infectious disease epidemic, quick identification and isolation of patients with actual and highly probable cases in a single ward in a hospital is essential to control the epidemic and to prevent the spread of infection in the hospital. To achieve this, some effective discriminatory authority during the course of the epidemic is very important.^{27,28}

The Taiwanese government implemented numerous intervention measures, including 2 levels of quarantine. Level A quarantine applied to people who potentially had contact with infectious individuals, and level B quarantine applied to travelers coming from affected areas abroad. More than 150,000 people were notified and placed under home quarantine, us-

ing limited contact tracing and border control measures. Only 24 of these quarantined individuals turned out to have SARS,¹⁰ which accounted for only 5% of all confirmed SARS cases. One should note, however, that full-scale (ie, level A and level B) quarantine in Taiwan was not implemented until April 28, when several major hospital-based infection clusters had already occurred.²⁷ Therefore, swift home quarantine of potentially exposed individuals and voluntary quarantine of individuals with subclinical symptoms should be considered. These could be effective complementary intervention measures to prevent people who are potentially infectious from spreading the epidemic further in the community. In addition, these measures could prevent hospitals from being overburdened with patients who have suspected cases that turn out not to be genuine. Such complementary measures are particularly relevant if no effective medical treatment is readily available during the early stages of emerging novel infectious diseases, as in the case of SARS in 2003 or the potential mutation of avian influenza virus (H5N1) to a strain that can be transmitted from person to person.

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APPENDIX A

The Model

Let $t = 1, 2, \dots, T$ be the time units (in days) for the data. Note that the first recognized SARS patient in Taiwan was a 54-year-old businessperson who traveled to Guangdong Province, China, on February 5, 2003, returned to Taipei via Hong Kong on February 21, and had onset of symptoms on February 25. Given that most estimates of the SARS incubation period are less than 8 days,¹⁶⁻¹⁸ it is therefore unlikely that the infection would have occurred before February 18, if we take into account of the length of the incubation period. Therefore, February 18 is assumed to be the start of the epidemic in Taiwan, and this date is denoted $t = 1$. The latest data available for analysis were from June 25, 2003, and thus T is set at 128 days.

Parameters

The variable μ_t indicates the expected number of individuals with onset of symptoms on day t . The λ_t variable indicates the expected number of infections on day t . The variable $f_{t,d}$ indicates the probability that an individual is infected on

day t and has an incubation period of d days. The variable $N_{t,d}$ indicates the number of individuals infected on day t with an incubation period of d days. The variable Y_t indicates the number of reported and/or confirmed cases on day t .

Assumptions

The daily numbers of infections are assumed to follow independent Poisson processes with intensities λ_t for $t = 1, \dots, T$. In addition, the daily numbers of confirmed and/or identified cases are assumed to follow independent Poisson processes with intensities

$$\mu_t = \sum_{s=0}^{t-1} \lambda_{t-s} f_{t-s,s}$$

for day t .

Because the incubation period is relatively short and the basic treatment is quarantine,¹⁰ the effect of the infection time d on the incubation period is minimal and may be ignored. Hence, $f_{t-s,s}$ is simplified as f_s .

APPENDIX B

Expectation-Maximization-Smoothing Algorithm (EMS)

There are 2 adequate fits to SARS-associated data sets, namely the Weibull and gamma distributions.^{4,18} The complete data log-likelihood function for λ_t is given as follows:

$$\log L = \sum_{t=1}^T \sum_{d=0}^{T-t} \{N_{t,d} \log(\lambda_t f_d) - \lambda_t f_d\}, \quad (1)$$

where f_d is assumed to follow either a gamma or a Weibull distribution, and the cumulative density functions are

$$F(t) = \frac{1}{\beta^\alpha \Gamma(\alpha)} \int_0^{t+0.5} x^{\alpha-1} e^{-x/\beta} dx$$

or

$$F(t) = 1 - \exp\left\{-\left[\frac{t+0.5}{\beta}\right]^\alpha\right\},$$

respectively. Unknown parameters (α, β) for the 2 distributions mentioned above can be estimated on the basis of the incubation-days of 98 patients, with their infection dates being identified retrospectively.

In practice, we can only observe Y_t . Mathematically, we have

$$Y_t = \sum_{d=0}^{t-1} N_{t-d,d}.$$

A convenient tool to estimate λ_t in a situation in which data are missing is the expectation-maximization (EM) algorithm. However, the estimates of λ_t may be very erratic, and the interpretation is generally made more sensible by smoothing out the estimates. Hence, the expectation-maximization-smoothing (EMS) algorithm⁶ was adopted in the current analysis, using the algorithm summarized below.

Expectation Step

The posterior expectation of $N_{t,d}$ given Y_1, \dots, Y_T can be shown to be

$$E(N_{t,d} | Y_1, Y_2, \dots, Y_T) = Y_{t+d} \frac{\lambda_t f_d}{\sum_{i=1}^{t+d} \lambda_i f_{t+d-i}}.$$

Maximizing Step

The maximum likelihood estimates of λ_t can be obtained by the iterative updating equations

$$\hat{\lambda}_t^{[j+1]} = \frac{\tilde{\lambda}_t^{[j]} \sum_{d=0}^{T-t} Y_{t+d} f_d}{\sum_{d=0}^{T-t} f_d \sum_{i=1}^{t+d} \tilde{\lambda}_i^{[j]} f_{t+d-i}},$$

where

$$\tilde{\lambda}_t^{[j]}$$

is the estimate of λ_t at the j -th iteration.

Smoothing Step

As the fluctuation among the observed daily number of SARS confirmed cases is not that erratic, we can simply adopt a 3-width window to smooth out the

$$\hat{\lambda}_t^{[j]}$$

in each iteration in the M-step. The corresponding weights are $w_0 = w_2 = 0.1$ and $w_1 = 0.8$. Therefore, we have

$$\tilde{\lambda}_t^{[j+1]} = \sum_{i=0}^2 w_i \hat{\lambda}_{[j+1]t+i-1}.$$

Hence, the smoothed estimate of λ_t is given by

$$\tilde{\lambda}_t = \lim_{j \rightarrow \infty} \tilde{\lambda}_t^{[j]}.$$

A gamma form for f_d yields a value of -403.01 for the log-likelihood function (1), whereas a Weibull form yields -501.23 , indicating that in the case of the Taiwan SARS outbreak, the incubation distribution is better fitted by the gamma distribution. The estimated mean duration (\pm SD)

of the incubation period for SARS in Taiwan is 6.33 ± 3.22 days. Donnelly et al.¹⁹ used a gamma distribution for data on the incubation period of SARS in Hong Kong, with an estimated mean duration (\pm SD) of 6.37 ± 4.09 days.

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