Richards Model: A Simple Procedure for Real-time Prediction of Outbreak Severity *

Ying-Hen Hsieh
Department of Applied Mathematics
National Chung Hsing University
Taichung 401, Taiwan
E-mail: hsieh@amath.nchu.edu.tw

Abstract

We propose to use Richards model, a logistic-type ordinary differential equation, to fit the daily cumulative case data from the 2003 severe acute respiratory syndrome outbreaks in Taiwan, Beijing, Hong Kong, Toronto, and Singapore. This model enabled us to estimate turning points and case numbers during each phases of an outbreak. The 3 estimated turning points are March 25, April 27, and May 24. Our modeling procedure provides insights into ongoing outbreaks that may facilitate real-time public health responses when faced with infectious disease outbreak in the future.

1 Introduction

Prediction of the future is a risky but tantalizing endeavor in any discipline in the scientific studies of natural phenomena, be it that of climate change, seismic movement, or occurrence of deadly diseases, not to mention the ascertaining of social phenomena such as economic trends and market volatility. In recent decades, the utilization of mathematical models in the the studies of infectious diseases (e.g., [2]) for the purpose of public health prevention and control has placed the predictive abilities of the models in high demanding, especially for newly emerging disease outbreaks where public health policy makers must decide on the best course of intervention measures as crucial scientific knowledge regarding the disease outbreak is being gathered and observations

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or theories can be tested as understanding of the phenomenon develops (e.g., [1, 30, 6, 23]). For novel infectious diseases such as the severe acute respiratory syndrome (SARS) outbreak of 2003, the importance of proper prediction of the disease severity at the early stages of the outbreak became even more evident [31, 4, 26, 10].

In a 1972 paper on predictions of future human populations, Keyfitz [16] made the distinction between two types of prediction. One is a "projection" which is a consequence of a set of assumptions; the other is a forecast, an unconditional statement of what will happen, albeit perhaps with a measure of the uncertainty. The two are related in the sense that, often, the methods for projection provide means with which forecasts are possible. In the aftermath of the SARS outbreak, for example, Massad et al. [23] attempted to analyze the distinction between forecasting and projection models as assessing tools for the estimation of the impact of intervention strategies, by providing a projection of what would have happened with the course of SARS epidemic if the universal procedures to reduce contact were not implemented in the affected areas.

In an endeavor to assess the effectiveness of intervention measures during the SARS pandemic, Zhou and Yan [38] used Richards model, a logistic-type model [32], to fit the cumulative number of SARS cases reported daily in Singapore, Hong Kong, and Beijing. In that article, they obtained estimates for the cumulative case number and basic reproduction number for each affected area. However, only partial case data during the outbreak was used which influenced the accuracy of the result. More seriously, the inflection point of the logistic curve, which could provide vital information pertaining to the changing trends of the epidemic and possibly indicating changes in intervention and control, was not discussed.

Hsieh et al. [12] proposed to use Richards model, along with the complete Taiwan SARS case data from the beginning of the outbreak to its end, to obtain an estimate of the accumulative case number. Moreover, the inflection point of the S-shaped epidemic curve was obtain which indicates the turning point of the outbreak in Taiwan when the daily number of infections starts to decrease. More recently, Hsieh and Cheng [14] use the SARS case data of Greater Toronto area (GTA) to demonstrate that even for a multi-staged epidemic, Richards model still can be used for real-time prediction of outbreak severity as well as real-time detection of turning points.

In this work, we will give a complete overview of Richards model as a useful tool for public health purposes of instantaneous ascertaining of a short and ongoing disease outbreak. We will introduce some basics of Richards model in the next section. In Section 3, we will demonstrate the use of model in outbreaks where the cumulative case curve exhibits an S-shaped curve by using the SARS data of Taiwan, Beijing, and

Hong. In Section 4 we will make use of the SARS data of GTA and Singapore to demonstrate that the same procedure can be used for real-time prediction of an outbreak with multiple waves. Finally, we give some remarks in Section 5.

2 Logistic and Richards Models

The logistic model was first proposed by Verhulst [34] in 1838 to model population growth after reading Thomas Malthus' *An Essay on the Principle of Population* [22]. The model equation, also known as Verhulst equation, is as follows:

$$I'(t) = rI[1 - \frac{I}{K}], \tag{2.1}$$

where $I(t)$ is the population size in question at time t, r is the intrinsic growth rate, and K is the "carrying capacity". In his 1995 book *How Many People Can The Earth Support*, Cohen [5] explained that Verhulst attempted to fit a logistic curve based on the logistic function to 3 separate censuses of the population of the United States of America in order to predict future growth. Interestingly, all 3 sets of predictions failed. This equation is also sometimes called the Verhulst-Pearl equation following its rediscovery by Pearl in 1920's (see, e.g., [28]). Pearl, together with Reed, used Verhulst's model to predict an upper limit of 2 billion for the world population. This was passed in 1930 [29]. A later attempt by Pearl and an associate Sophia Gould in 1936 then estimated an upper limit of 2.6 billion. This was passed in 1955. Alfred J. Lotka also derived the equation again in 1925, calling it the law of population growth [20].

In 1959, Richards [32] proposed the following modification of the logistic model to model growth of biological populations:

$$I'(t) = rI[1 - (\frac{I}{K})^a]. \tag{2.2}$$

The additional of the parameter a provide a measure of flexibility in the curvature of the S shape exhibited by the resulting solution curve. As a model for the growth of an epidemic outbreak, $I(t)$ is the cumulative number of infected cases at time t in days, K is the carrying capacity or total case number of the outbreak, r is the per capita growth rate of the infected population, and a is the exponent of deviation from the standard logistic curve. Unlike models with several compartments commonly used to predict the spread of disease, the Richards model considers only the cumulative infective population size with saturation in growth as the outbreak progresses, caused by decreases in recruitment because of attempts to avoid contacts (e.g., wearing facemask) and implementation

of control measures. The basic premise of the Richards model is that the daily incidence curve consists of a single peak of high incidence, resulting in an S-shaped epidemic curve and a single turning point of the outbreak. These turning points, defined as times at which the rate of accumulation changes from increasing to decreasing or vice versa, can be easily located by finding the inflection point of the epidemic curve, the moment at which the trajectory begins to decline. This quantity has obvious epidemiologic importance, indicating either the beginning (i.e., moment of acceleration after deceleration) or end (i.e., moment of deceleration after acceleration) of a phase.

The analytic solution of (2.2) is

$$I(t) = K/[1 + e^{-r(t-t_m)}]^{1/a}. \tag{2.3}$$

It is trivial to show that t_i is the only inflection point (or turning point denoting deceleration after acceleration) of the S-shaped epidemic curve obtained from this model. Moreover, $t_m = t_i + (\ln a)/r$ in (2.3) is equal to the inflection point t_i when $a = 1$, and approximates t_i when a is close to 1.

3 Single Wave Outbreak

The Richards model fits the single-phase SARS outbreak in Taiwan [12] well. We give below the parameter estimation results and the theoretical epidemic curve for Taiwan SARS outbreak of February 23-June 12, 2003, using Richards model from [12] in Table 1 and Figure 3.1, respectively. The result indicated that the infection occurred on May 3, and the estimate for the maximum case number of $K = 343.3$ [95%CI: (340, 347)]is merely 0.8% off the actual total case number of 346. Moreover, the case number data used was sorted by onset date. Given a mean SARS incubation of approximately 5 days [37], the inflection point for SARS in Taiwan could be traced back to 5 days before May 3, namely April 28. On April 26, the first SARS patient in Taiwan died. Starting April 28, the government implemented a series of strict intervention measures, including household quarantine of all travellers from affected areas [17]. In retrospect, April 28 was indeed the turning point of the SARS outbreak in Taiwan.

It is also interesting to note that, using this method, relatively accurate estimates for the turning point of the epidemic and the final epidemic size can be obtained fairly early [14]. In this instance, estimate of turning point on May 3 can be obtained using case data of up to May 10, while CI interval for total case number of (298, 370) is obtained using data up to May 15. This indicates that, if no deviation from the actual events had occurred, the authority could detect the turning point (for

Table 1: Estimates of parameters in Richards model using cumulative confirmed SARS case data in Taiwan (N=346) of selected time periods. t_m=66.6 implies the turning point of epidemic is May 3. (Source: [12])

Time Period	t_m	r	a	K	95% C.I.
$2/25-4/28$	78.2193	1.1421	10.0632	875.8	$(0^*, 147247)$
$2/25-5/05$	65.5108	0.5343	4.7745	204.9	$(185.2, 224.6)$
$2/25-5/10$	66.9819	0.2737	2.4169	253.1	$(232.1, 274.2)$
$2/25-5/15$	67.508	0.1483	1.2326	334.2	$(298.2, 370.2)$
$2/25-5/20$	67.432	0.1419	1.1694	342.1	$(321.5, 362.6)$
$2/25-6/15$	66.6187	0.1359	1.0731	343.4	$(339.7, 347.1)$

*max(0, lower bound)

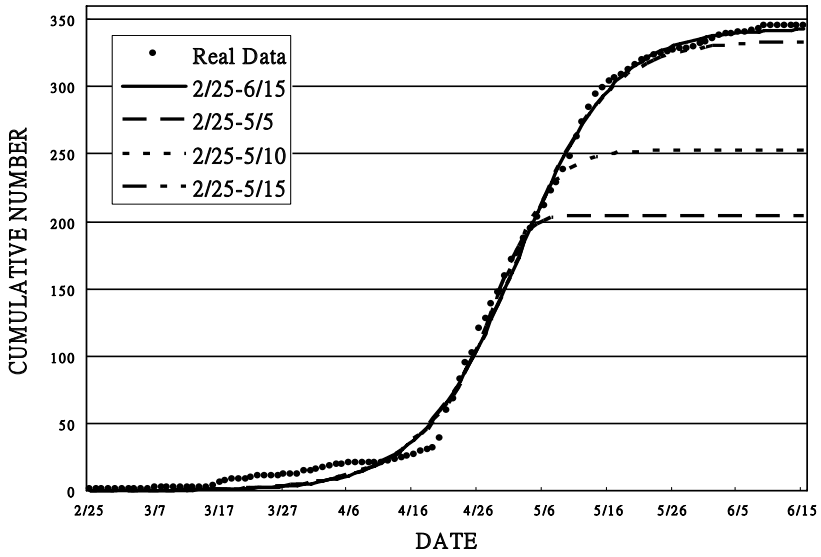

Figure 3.1: The theoretical epidemic curve for Taiwan SARS outbreak of February 23-June 12, 2003, using Richards model. Turning point is May 3. (Source: [12])

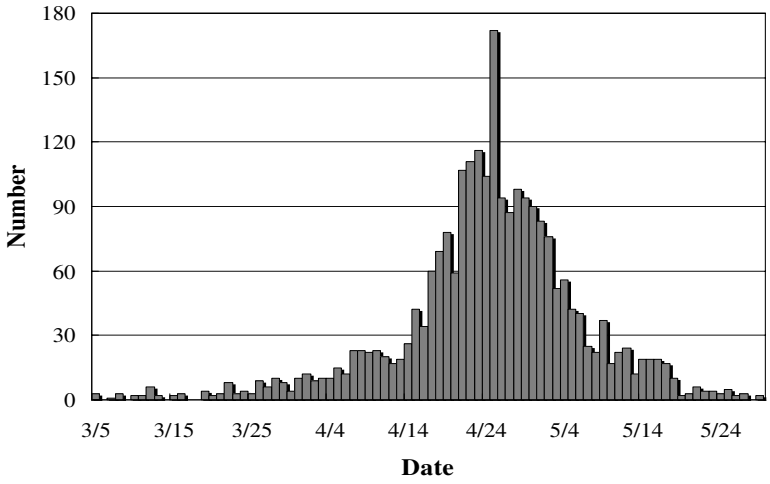

Figure 3.2: The daily SARS incidence curve by hospitalization date for Beijing SARS outbreak of March 3-May 29, 2003. (Source: [18])

the better) of the outbreak about one week after its occurrence. Furthermore, a range for the final epidemic size could be estimated a month before the end of the outbreak. The real-time predictive potential of this procedure will be discussed in more details in the Conclusions section. We also note that although we did use the additional laboratory confirmed case data in Taiwan as detailed in [13], estimation studies have shown that the accuracy of the procedure will not be compromised even if we did use the additional case data.

For the purpose of illustration and comparison, we perform the same procedure to the SARS data from other affected areas. During the 2003 epidemic, the largest outbreak of SARS occurred in Beijing in the spring of 2003. Multiple importations of SARS to Beijing initiated transmission in several healthcare facilities. The outbreak in Beijing began March 5, and by late April daily hospital admissions for SARS exceeded 100 for several days. According to [18], total 2,521 cases of probable SARS occurred. We reconstruct the daily incidence data from epidemic curve given in Figure 1 of [18] and obtain the incidence data of 2380 cases with hospitalization dates between March 5 to May 29 in Figure 3.2.

Table 2: Estimates of parameters in Richards model using cumulative confirmed SARS case data of 2380 cases in Beijing during March 5-May 29, 2003. t_i=51.92 implies the turning point of epidemic is April 26.

Period	r	a	t_m	t_i	K	95% C.I.
$3/5-4/25$	0.846	7.62	78.14	75.74	25385.5	$(0^*-7012482.0)$
$3/5-4/30$	0.751	6.77	54.30	51.75	1798.1	$(1707.7-1888.4)$
$3/5-5/05$	0.398	3.53	55.41	52.24	2097.3	$(2039.6-2155.0)$
$3/5-5/10$	0.321	2.80	55.47	52.27	2198.5	$(2164.3-2232.7)$
$3/5-5/15$	0.274	2.33	55.27	52.19	2264.7	$(2238.2-2291.2)$
$3/5-5/20$	0.242	1.98	54.90	52.07	2315.3	$(2291.9-2338.6)$
$3/5-5/29$	0.219	1.74	54.45	51.92	2351.8	$(2334.8-2368.8)$

*max(0, lower bound)

We also note that the official cumulative case number in Beijing is 2631 as published by World Health Organization (WHO) website (see [25] or [36]).

The data was used to estimate the parameters in Richards model. The parameter estimates and the resulting theoretical epidemic curve are given in Table 2 and Figure 3.3, respectively.

The estimate for total case number of $K = 2352$ [95%CI: (2335, 2369)] is somewhat less accurate than that of Taiwan SARS, perhaps due to the fact that not all probable cases (totaling 1521) were accounted for in the data used. Moreover, the epidemic curve data of Beijing was given by hospitalization date, which was affected by variance in the time it took for each case to be hospitalized, also could result in inaccuracy in the estimates. Assuming that it takes at least 24 hours for a symptomatic SARS case to be hospitalized (see e.g., [13]), the turning point of April 26 by hospitalization date leads us to conclude that the turning point for SARS infections in Beijing had occurred on or before April 20. It is interesting to note that, on April 17, 123 fever clinics were set up in all secondary and tertiary hospitals in Beijing to monitor suspected SARS cases with onset of symptoms [27]. Perhaps more importantly, on April 20, the outbreak was announced publicly by the Chinese government for the first time, thus alerting the domestic population as well as the international community to the presence of this possibly fatal infectious disease epidemic, most likely leading to

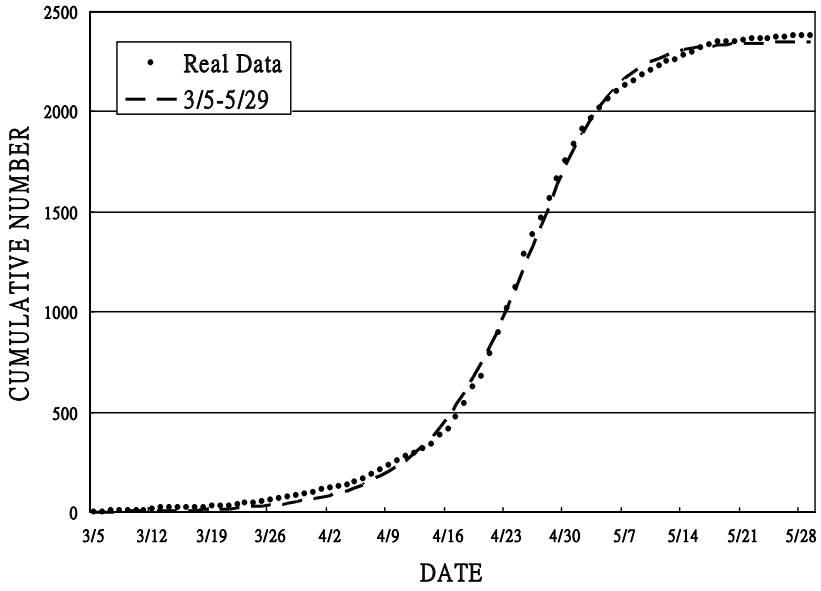

Figure 3.3: The theoretical epidemic curve for Beijing SARS outbreak of March 3-May 29, 2003, using Richards model. Turning point is April 26.

improved infection control and decrease in contact rate. We again note that, similarly accurate estimation results can be obtained using only data from March 5 to May 5, merely 10 days after the actual turning point around April 26.

Next we turn our attention to Hong Kong, where the second largest clusters of SARS infections occurred. Using the official epidermic curve data by onset date from the Hong Kong Department of Health website, we fit the cumulative case data of 1755 total cases from February 15 to May 31 to Richards model and obtained the resulting parameter estimates in Table 3 with the corresponding theoretical epidemic curve in Figure 3.4. The estimated final epidemic size of $K = 1742$ [95%CI: (1730, 1753)] shows a slight underestimate, perhaps due to the presence of multiple superspreading events (SSEs) in Hong Kong [33]. The turning point of March 26 implies the turning point for infections had occurred by March 21. Riley et al. [33] estimated that the Amoy Gardens SSE, at the peak of the outbreak in Hong Kong, had occurred on March 19 (95%CI, March 18 to March 20) and had infected 331 [95% CI: (295, 331)] people. Moreover, they also estimated that the estimated reproduction number at time t in the absence of SSEs, defined to be the average number of infections caused by one typically infectious individual at time t excluding SSEs and denoted by R_t^{XSS}, dropped sharply to 1.0 [95% CI: (0.7, 1.2)] by 21 March, which can be attributed to increased awareness of the infection by the general population, leading to voluntary drops in contact rates and to improved control measures in hospitals. However, control measures such as school closures and recommendations against unnecessary travel could also have played an important role. Here the turning point can be detected using data of February 15 to April 21, almost one month after its occurrence.

4 Outbreaks with Multiple Waves

All of the previous examples exhibit a single S-shaped epidemic curve, indicating one wave of infection. However, the SARS outbreak in the greater Toronto area (GTA) in Canada during February 23 to June 6 was know to have two phases. recently, Hsieh et al. [14] proposed a multi-staged Richards model, a variation of the S-shaped Richards model, which makes a distinction between two types of turning points. Other than the previous inflection point of the S curve, there is a second type of turning point in a multi-wave epidemic curve where the growth rate of the number of cumulative cases begin to increase, which signals the beginning of the next wave. For a multistage Richards model, one stage for each of the S-shaped segments results from the multiple waves of infection during this outbreak. Stages are distinguished by turning

Table 3: Estimates of parameters in Richards model using cumulative confirmed SARS case data in Hong Kong during February 15-May 31, 2003. t_i=38.76 implies the turning point of epidemic is March 26.

Period	r	a	t_m	t_i	K	$95\%C.I.$
$2/15-4/01$	0.593	4.83	41.92	39.27	1074.4	$(969.1-1179.7)$
$2/15-4/11$	0.180	1.19	40.61	39.65	1452.3	$(1372.5-1532.1)$
$2/15-4/21$	0.123	0.61	35.66	39.62	1625.7	$(1575.2-1676.1)$
$2/15-5/01$	0.108	0.43	31.56	39.40	1685.7	$(1655.8-1715.6)$
$2/15-5/11$	0.100	0.33	28.18	39.18	1713.3	$(1639.5-1733.1)$
$2/15-5/21$	0.095	0.26	24.85	38.96	1731.0	$(1716.4-1745.6)$
$2/15-5/31$	0.092	0.21	21.96	38.76	1741.8	$(1730.4-1753.3)$

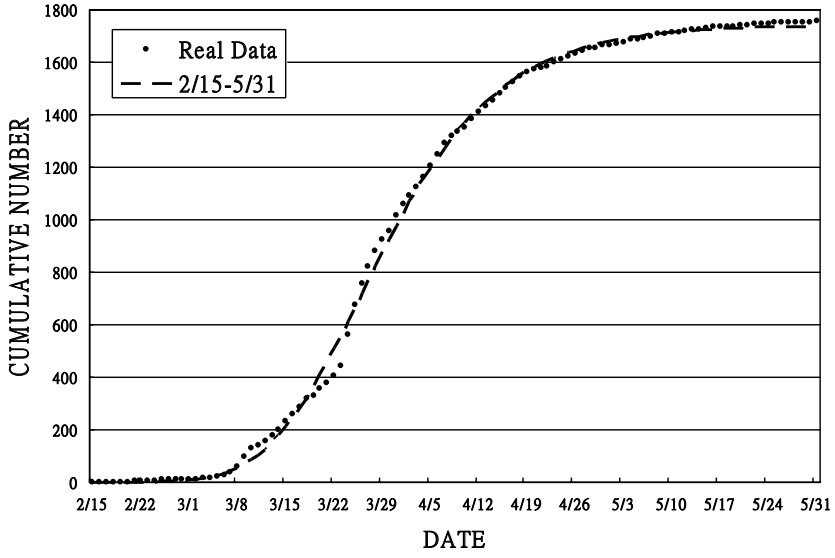

Figure 3.4: The theoretical epidemic curve for Hong Kong SARS outbreak of February 15-May 31, 2003, using Richards model. Turning point is March 26.

points (or inflection points), denoting acceleration after deceleration at the end of each S-shaped segment, the local minima of the corresponding incidence curves. For an n-phase epidemic outbreak, n-1 local minima separate the n phases. For illustration, the incidence curve for GTA contains two peaks (local maximum or turning point of the first type) and one valley (local minimum or turning point of second type).

The multistage Richards model procedure requires the following five steps:

1. Fit the Richards model to cumulative cases on successive days by using a standard least-square routine. For single-phase outbreaks, parameter estimates (a, r, t_i, K) will converge as the trajectory approaches the carrying capacity K, as demonstrated in the Taiwan, Beijing, and Hong Kong SARS outbreaks.
2. If estimated parameters remain convergent until no more new cases are detected, the outbreak has only one phase. However, if the estimates begin to diverge from heretofore fixed values, one knows that a turning point denoting the start of a second phase has occurred.
3. Locate the turning point, t_{min}, separating two S-shaped phases of the epidemic as the local minimum of the incidence curve. This is the curve for $I''(t)$ given in the equation (2.2).
4. Fit the Richards model to the cumulative case curve again, but starting from $t_{min} + 1$, the day after the start of second phase. The estimated parameters (a, r, ti, K) will again converge as the curve approaches the carrying capacity K for the second phase.
5. Repeat steps 2-4 in the event more phases occur until the outbreak ends.

By considering successive S-shaped segments of the epidemic curve separately, one can estimate the maximum case number, K, and locate the turning points, thus providing an estimate for the cumulative number of cases during each phase. Using this procedure and the GTA daily SARS case number by onset date obtained from the Public Health Agency of Canada (PHAC) website (http://www.phac-aspc.gc.ca/sarssras/ pdf-ec/ec_ 20030808.pdf), the parameter estimates of the two waves of the GTA outbreak were obtained in [14] and given below in Tables 4 and 5, with the corresponding theoretical epidemic curve give in Figure 4.1.

The number of cases during the first phase ending on April 27 (or April 26) is 143 (see Table 4), well approximated by our estimate for the carrying capacity, $K = 144.14$ [95%CI: (142.19, 146.09)]. Note that the number of 142 has been added to the estimates for K and its 95% confidence interval (see [14]). The turning point of March 25 indicates

Table 4: Parameter estimates for Phase 1 of GTA outbreak (2/23-4/27, total number of cases is 143). t_i=30.35 implies the turning point of the first phase is March 25. (Source: [14])

Time Period	r	a	t_m	t_i	K	95% C.I.
$2/23-3/25$	0.859	4.835	26.93	25.09	60.10	54.71-65.49
$2/23-4/04$	0.146	0.689	27.51	30.06	140.53	115.88-165.17
$2/23-4/14$	0.152	0.773	28.81	30.50	142.78	137.34-148.22
$2/23-4/24$	0.147	0.718	28.19	30.45	143.99	141.76-146.21
$2/23-4/26$	0.146	0.710	28.08	30.43	144.14	142.19-146.09
$2/23-4/27$	0.146	0.710	28.08	30.43	144.14	142.19-146.09
$2/23-4/28$	0.146	0.709	28.08	30.43	144.14	142.42-145.86
$2/23-4/30$	0.144	0.693	27.86	30.40	144.41	142.85-145.96
$2/23-5/02$	0.142	0.664	27.47	30.35	144.84	143.40-146.29

the turning point of the first wave of infection occurred around March 20. Satisfactory estimates for case number and turning point can be obtained using epidemic data of up to April 4, 10 days after the turning point had occurred. The divergence of parameter estimates soon after April 28 indicates that the second turning point had occurred around April 27, or the start of second wave of infections five days earlier on April 22. Our results corroborate the assessment of Health Canada, which pinpointed April 21 as the start of the second phase of the outbreak [35].

The parameter estimation of the second phase yields the estimated case number of 249 [95%CI: (247, 250)], exactly the actual case number in the GTA outbreak. The estimated turning point $t_i = 26.36$ pinpoints to May 24, or a turning point for SARS infections 5 days earlier on May 19. This finding further corroborates Health Canada's assertion that, among the 79 cases that resulted from exposure at the hospital where the index patient of the second phase stayed, 78 had exposures that occurred before May 23 [35]. Note also that good estimates can obtained by using data that end just 3 days after the turning point, on May 27, giving an accurate prediction ($K = 244.36$ [95%CI: 240.53-268.18]) of the actual cumulative case number.

Zhou and Yan [38] had shown that Richards model fits the single-phase SARS outbreaks in Hong Kong and Beijing well, but not as sat-

Table 5: Parameter estimates for Phase 2 of GTA outbreak (4/28-6/6, cumulative number of cases is 249). t_i=26.37 corresponds to the turning point of the second phase on May 24. (Source: [14])

Time Period	r	a	t_m	t_i	K	95% C.I.
$4/28-5/25$	0.557	3.866	27.02	24.59	223.37	199.67-247.07
$4/28-5/27$	0.350	2.393	28.33	25.84	244.36	220.53-268.18
$4/28-5/29$	0.236	1.554	29.22	27.36	271.28	240.94-301.62
$4/28-5/31$	0.321	2.202	28.88	26.43	252.53	244.32-260.74
$4/28-6/02$	0.352	2.448	28.90	26.36	249.51	245.70-253.33
$4/28-6/04$	0.359	2.508	28.92	26.36	248.96	246.67-251.25
$4/28-6/06$	0.367	2.576	28.95	26.37	248.52	246.98-250.07

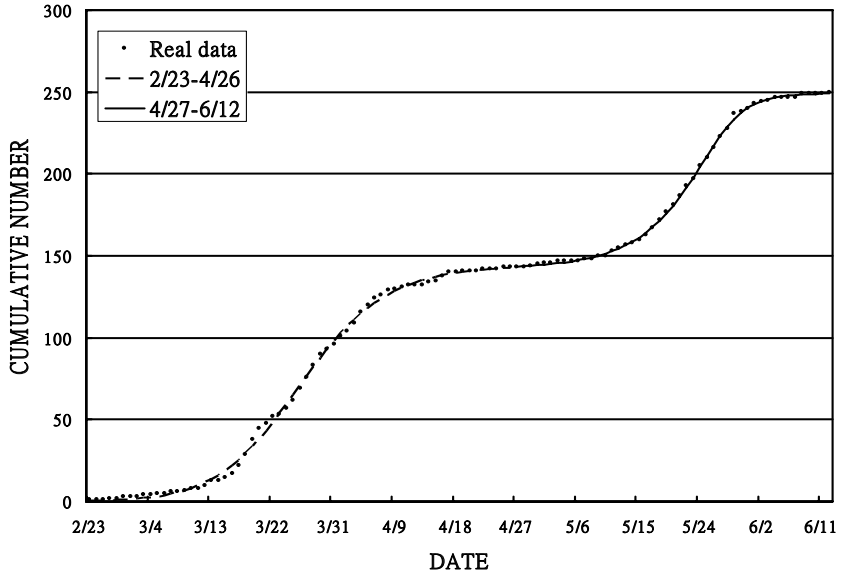

Figure 4.1: The theoretical epidemic curve for GTA SARS outbreak of February 23-June 6, 2003, using Richards model. Turning points are March 25, April 27, and May 24. (Source: [14])

Table 6: Parameter estimates for Phase 1 of Singapore outbreak (2/25-3/28, total number of cases is 103). t_i=19.28 implies the turning point of the first phase is March 16.

Time Period	r	a	t_m	t_i	K	95% C.I.
$2/25-3/21$	0.271	8.771	35.763	27.74	47.06	0*-32212.20
$2/25-3/23$	0.999	5.157	21.410	19.77	88.16	84.45-91.86
$2/25-3/25$	0.646	3.217	21.374	19.57	93.20	89.11-97.29
$2/25-3/26$	0.524	2.526	21.223	19.45	96.14	91.70-100.60
$2/25-3/27$	0.432	1.999	20.950	19.35	99.27	94.41-104.10
$2/25-3/28$	0.382	1.701	20.669	19.28	101.50	96.68-106.40
$2/25-3/29$	0.329	1.385	20.18	19.19	104.50	99.29-109.80

*max(0, lower bound)

isfactorily for the Singapore outbreak. Here we fit the Singapore daily SARS case data by onset date, obtained from Singapore Ministry of Health (MOH) website, to the multi-staged Richards model. The results are given in Tables 6 and 7, and Figure 4.2.

The first wave corresponds to the hospital cluster at Tan Tock Seng Hospital (TTSH), a 1400-bed acute care hospital [15], where 105 total secondary cases occurred between March 4 to April 5 [3]. The number of cases during the first phase ending on March 28 of 103 is again well approximated by our estimated carrying capacity, $K = 101.50$ [95%CI: (96.68, 106.40)], using the case data of up to March 28. The turning point of March 16 indicates the turning point of the first wave of infection occurred around March 11. We note that in TTSH, isolation of infectious cases and admission of any new suspected or probable cases to isolation facilities were implemented from March 13. Moreover, one of the infected healthcare workers (HCWs) at TTSH (index case B in [8]) with onset of symptoms on 7 March and provisionally diagnosed to have dengue fever, later was admitted on 10 March to Ward 8A where she in turn infected 21 persons before she was isolated on March 13. On the same day, the Singapore MOH alerted all hospitals and doctors to look out for cases of pneumonia who had recently travelled to Hong Kong, Hanoi or Guangdong province [8]. The MOH also advised travellers returning from these areas to seek medical attention if they developed flu-like symptoms, all of which helped to alleviate the spread of SARS

Table 7: Parameter estimates for Phase 2 of Singapore outbreak (3/28-5/05, total number of cases is 204). t_i=8.56 implies the turning point of the second phase is April 6.

Time Period	r	a	t_m	t_i	K	95% C.I.
$3/28 - 4/15$	0.181	0.003	-22.76	9.21	192.80	0*-324.50
$3/28 - 4/20$	0.170	0.021	-14.18	8.46	200.79	181.00-220.60
$3/28 - 4/25$	0.162	0.027	-13.49	8.79	203.90	192.86-214.90
$3/28 - 4/30$	0.162	0.024	-13.92	8.94	204.10	197.27-210.90
$3/28 - 5/05$	0.16	0.02	-15.83	8.56	203.50	200.14-206.90

*max(0, lower bound)

infections.

Satisfactory estimates for case number and turning point can be obtained using epidemic data around 10 days after the turning point had occurred. Here, the divergence of parameter estimates soon after March 28 indicates that the second turning point had occurred around March 28, or the start of second wave of infections occurred five days earlier before March 22. The second wave could probably be attributed to multiple events. One such event is index case D in [8], a 60-year-old ex-patient of TTSH who was admitted on 5 March to Ward 5A (the same ward as index case A) at TTSH, and discharged on 20 March with no clinical manifestations of SARS. He was readmitted to an open ward (Ward 57) at Singapore General Hospital (SGH), on 24 March for steroid-induced gastrointestinal bleeding and a diabetic foot ulcer. It was only on 5 April when chest x-ray showed evidence of pneumonia that he was clinically diagnosed as a probable SARS case, by which time several family members and HCWs in the wards he stayed in had been identified [8]. Another is a 90-year-old woman (index case F in [8]) who had been warded next to a SARS patient in Ward 7D in TTSH on March 16-17, was discharged to a private nursing home (Orange Valley Nursing Home) and then admitted to Changi General Hospital (CGH) on March 25 when she subsequently fell ill again with breathing difficulty. This index case led to a small cluster of 7 cases linked to the nursing home and CGH.

The parameter estimation of the second phase yields the estimated case number of 203.50 [95%CI: (200.14, 206.90)], exactly the actual case number of 204 in the Singapore outbreak. Again, the number of 102 has been added to the estimates for K and its 95% confidence interval. The

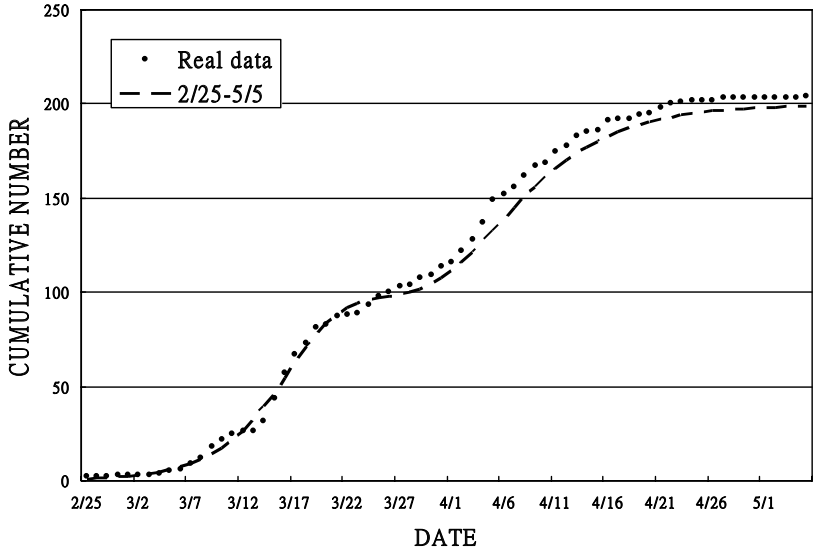

Figure 4.2: The theoretical epidemic curve for Singapore SARS outbreak of February 25-May 5, 2003, using Richards model. Turning points are March 16, March 27, and April 6.

estimated turning point pinpoints to April 6, or a turning point for SARS infections 5 days earlier on April 1. By this time, multiple intervention and control measures had already been in place. On March 26, decision taken to close all childcare centers, pre-schools, primary and secondary schools, junior colleges, centralized institutes and madrasahs from 27 March 2003 to 6 April 2003. Other measures taken during this time period include the establishment of an Inter-Ministry Working Group on March 28 to look into further measures to contain SARS; the Civil Aviation Authority of Singapore (CAAS) directing all airlines at Changi Airport to ask departing passengers the three WHO-recommended questions on symptoms of SARS and contact history before departure with health alert notice given to inbound passengers from affected areas starting on arch 30; and from March 31 on, for all inbound flights from affected areas, nurses were stationed to check passengers who appeared unwell and those with fever sent to TTSH for assessment (see the Appendix in [8]). Although by that time (march 28) the second wave had already started, which was unknown to the authority, these measures contributed to containing the second phase.

5 Conclusions and Remarks

The Richards model fitted all data well, allowing us to study retrospectively the significance of various events occurring at different times in each affected area during the SARS outbreak. Through this procedure, we can pinpoint retrospectively the key turning points for the spread of disease during a single- or multi-phase outbreak. Given incidence by onset or hospitalization date during the outbreak, one can use our procedure to forecast the eventual severity of current phases of the outbreak in real-time by estimating the carrying capacity, K. However, accuracy depends on having the incidence data for some time past the inflection point t_i and no new waves of infection in the future. However, when a new wave occurs, the divergence in the estimation will immediately alert us to the occurrence of a turning point of second type, as demonstrated with the GTA and Singapore multi-phase outbreak in Section 4. Furthermore, such estimates are possible shortly after the inflection point (or turning point) had occurred. In Table 8, we give a summary comparison of the date when the case data used will be sufficiently accurate to pinpoint the turning point of the current outbreak, as well as the estimated final case number.

Several observations can be drawn from the table. First, in most cases, the turning point was detected around ten days after it had occurred. The exceptions are Hong Kong, which took almost one months, and the second phase of GTA, which took only 3 days. The former can

Table 8: Comparison of estimated turning points and total case numbers (rounded off to integers) in SARS affected areas in 2003.

Affected area (duration)	turning point	case no.	estimation date	estimate (95%CI)
Taiwan (2/25-6/15)	5/3	346	5/15	334 (298, 370)
Beijing (3/3-5/29)	4/26	2380	5/5	2097 (2040, 2155)
Hong Kong (2/15-5/31)	3/26	1755	4/21	1626 (1575, 1676)
GTA 1 (2/23-4/27)	3/25	143	4/4	141 (116, 165)
GTA 2 (4/28-6/6)	5/24	249	5/27	244 (221, 268)
Singapore 1 (2/25-3/28)	3/16	103	3/27	102 (97, 106)
Singapore 2 (3/28-5/5)	4/6	204	4/25	204 (193, 215)

be explained by the fact that the spread of disease continue to persist even after the turning point on March 26 and did not end until more than two month later on May 31. The short amount of time it took for turning point to be detected seems to indicate the decisive nature of the intervention measures implemented (see previous section for a discussion) as the GTA outbreak ended within 13 days on June 6 after the turning point (May 24) had occurred.

The estimates of the total case numbers are quite accurate, with the exception of Beijing, and perhaps Hong Kong to a less degree. As mentioned earlier, the inaccuracy in Hong Kong estimation is probably caused by the superspreading event at Amoy Gardens, whose feature was not captured by Richards model. The inaccuracy in the Beijing estimation is most likely caused by the use of case data by hospitalization date, which resulted in loss of information on the actual spread of infections. This highlights the importance of swift and accurate data collection, especially for the purpose of real-time prediction.

We further note that, although the outbreak in each affected area occurred almost simultaneously within a time period of a little over two weeks, the turning points varied significantly. In that respect, Singapore seemed to have responded most swiftly and the outbreak there would have ended quickly with minimal loss if not for the second wave of infections in several hospital clusters due to undetected cases. The same can be said, to some degree, of the outbreak in GTA as well, which underscore the importance of swift identification and correct diagnosis when

Table 9: Comparison of basic reproduction numbers R_0 for SARS in some affected areas in literature computed using Richards model and generation time of SARS infection T=8.4 (Lipsitch et al. [19])

Affected area	Reference	r	R_0
Taiwan	Hsieh et al. [12]	0.136	3.08
Beijing	Zhou and Yan [38]	0.16	3.8
Beijing	[this article]	0.219	6.29
Hong Kong	Zhou and Yan [38]	0.09	2.1
Hong Kong	[this article]	0.092	2.17
Singapore	Zhou and Yan [38]	0.12	2.7
Singapore (phase 1)	[this article]	0.382	24.7
GTA (phase 1)	[this article]	0.146	3.41

faced with a novel infectious disease.

The results of the parameter estimation can also be used to compute the basic reproduction number R_0, or the average number of infections caused by one typically infectious individual in an entirely susceptible population, for each outbreak by using the formula $R_0 = exp[rT]$, where T is the duration of infectiousness. Using $T = 8.4$ from [19], we construct Table 9 to compare the affected areas. The results for the second phases of GTA and Singapore outbreaks are not valid for the purpose of initial stage estimation, due to the nature of multi-phase outbreak which distorts the the epidemiologic parameters (contact rate and transmission probability) of the initial phase.

The estimates of R_0 for Hong Kong from both [38] and this article agree almost exactly, and within range of the estimate of 2.7 [95%CI: (2.2, 3.7)] for the basic reproduction number excluding SSEs, R_0^{XSS}, in [33]. However, the results for Beijing differs significantly. For Beijing, since we have used the complete Beijing case data by hospitalization date in this work, while [38] only used partial Beijing case data from April 21 on, it is reasonable to suggest that the loss of information from the daily incidence data of March 3 to April 20 had an effect on the accuracy. Furthermore, it can be deduced that the loss of information on the initial explosive nature of the outbreak in Beijing led to a significant underestimate of the basic reproduction number. The larger basic reproduction numbers for Taiwan as compared with Hong Kong may be attributable to the relatively higher percentage of nosocomial infections

in Taiwan [9].

The estimates of R_0 for phase 1 of Singapore outbreak differ significantly, 2.7 in [38] compare to our estimate of 24.7. We note that it has been reported in an epidemiological study of Singapore SARS outbreak [8] that the first four index cases (index cases A, B, and C in [8]) in Singapore can be directly traced to have infected, respectively, 21, 22, and 26 cases by March 20 when index patient C was isolated. Hence our unusually high estimate might be a reasonable reflection of a series of superspreading events which had occurred during the initial stage of the Singapore outbreak (as opposed to the superspreading event of community infection cluster at Amoy Gardens in Hong Kong, which happened when the outbreak was already well underway). On the other hand, the estimate by [38] was obtained using the Singapore onset data after March 17, by which time most of the infections caused by the first three index cases (A, B, and C) had already occurred [8].

This further demonstrates the difficult dilemma of dealing with stochastic superspreading events [7], especially for real-time forecasts. The fact that our result for basic reproduction number of Singapore SARS outbreak seems to capture the impact of SSEs occurring at the early stages of the outbreak, while our result for Hong Kong agrees with the estimate by [33] of the basic reproduction number excluding SSEs in Hong Kong, where SSEs occurred in the later stages of the outbreak there, offers hope that simple models can indeed be useful, when properly utilized.

Mathematical models have been used to predict the course of epidemics, albeit with mixed results [24]. The easily implemented procedure, which can be run with any commercially available software which includes a subroutine for nonlinear least-square estimation, described can be extended to analysis of turning points and severity of multiphase epidemics while ongoing. During an outbreak such as SARS, to which available data were limited and uncertain, a simple model that requires only the most basic and perhaps only easily obtainable data under these circumstances offers our best chance to a practical solution to the understanding, prediction, and timely control of the outbreak. However, one must understand that mathematical models do not provide accurate numerical predictions and can be used to forecast only in fairly gross terms [21]. The accuracy of predictions depends heavily also on the assumption that no stochastic events occur in the remaining days that could significantly alter the course of the current phase of an outbreak. Detecting the occurrence of a second turning point or start of a second phase, as outlined in Step 2 of our multi-staged Richards model procedure in Section 4, is especially useful as it allows us to recognize early that an epidemic is worsening, as demonstrated here with GTA and Singapore SARS. Though predicated on the availability and accuracy of

case onset data, this procedure could be a valuable tool to public health policymakers for responding to future disease outbreaks with multiple turning points.

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