VOLUME 14 SUPPL. 1 PP 92–100 NOVEMBER 2009

Mathematical modelling of SARS and other infectious diseases in China: a review

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Summary

OBJECTIVE To give an overview of the recent history of publications on mathematical modelling of infectious diseases in the Chinese literature, and a more detailed review of the models on severe acute respiratory syndrome (SARS).
METHOD Literature review through the Chinese CAJ full-text database.
RESULTS The number of Chinese publications on mathematical modelling has at least quadrupled since the SARS epidemic in 2003. This increase not only included papers on SARS, but also on various other infectious diseases, indicating a substantial expansion of modelling experience in China. Typical problems of most studies were poor availability of data and lack of involvement of disease experts and decision-makers rendering the studies less useful for policies on control.
CONCLUSIONS We expect that the recent experience on modelling and current better access to and exchange of epidemiological data have paved the way for a more substantial role of this discipline during possible future outbreaks of infectious diseases. By making Chinese modelling initiatives more visible to non-Chinese readers, we hope to attract more international collaborators.

keywords review, mathematical modelling, infectious diseases, severe acute respiratory syndrome, China

Introduction

Mathematical modelling plays an important role in understanding the complexities of infectious diseases and their control. Modelling can be beneficial for studying the mechanisms underlying observed epidemiological patterns, assessing the effectiveness of control strategies, and predicting epidemiological trends. The study of the transmission dynamics of an infectious agent can be based on various types of mathematical frameworks, ranging from relatively simple curve fitting techniques to standard susceptible-infected-recovered (SIR) compartmental models (Anderson & May 1991; Diekmann & Heesterbeek 2000) to complex comprehensive stochastic individual-based models using computer simulation (Ferguson *et al.* 2005; Longini *et al.* 2005). Two important concepts in modelling outbreaks of infectious diseases are the basic reproductive number R_0 (the average number of secondary cases produced by a typical primary case in an entirely susceptible population) and the generation time (the average time from symptom onset in a primary case to symptom onset in a secondary case), which jointly determine the likelihood and speed of epidemic outbreaks (Anderson & May 1991; Diekmann & Heesterbeek 2000; Wallinga & Teunis 2004). All modelling efforts depend to a large degree on the availability of data about the infectious disease under study, so as to provide robust estimates of the parameters and their distribution.

A typical phenomenon is the rapid growth of literature on mathematical modelling in case of emergence of a new infectious disease. Modelling can relatively quickly meet the need for assessment of the potential long-term impact of such a disease, and it offers a means for evaluation and prediction of the effect of possible interventions, even with limited data available. Typical examples are the abundance of early models for (HIV) in the 1980s (Anderson 1988), and more recently those for pandemic influenza (Ferguson *et al.* 2005; Longini *et al.* 2005), Bovine spongiform encephalopathy (BSE) (Ferguson *et al.* 1997), and Creutzfeldt–Jakob Disease (CJD) (Bishop *et al.* 2006). Also after the outbreak of severe acute respiratory syndrome (SARS) in 2003, a large number of modelling papers on this emerging infectious disease appeared in the international literature. Bauch *et al.* (2005) gives an overview of all SARS models published during the period of the epidemic up to 2 years thereafter.

China also has a tradition in using mathematical modelling of infectious diseases. However, most of these studies are published by Chinese in Chinese journals, making them poorly accessible to international researchers. In China, where the SARS epidemic has hit hardest, it has led to various initiatives to understand more about this disease. The government has invested substantially in the establishment of scientific studies on SARS and other emerging infectious diseases, with the aim to help its own population and at the same time to catch-up with the international scientific level. These studies include mathematical modelling and setting up countrywide surveillance systems for real-time data collection. Apart from the studies by Wang and Ruan (2004) and Bai and Jin (2005), all SARS modelling studies were published in Chinese.

In this paper we give an overview of the recent history of Chinese publications on infectious diseases that use mathematical modelling. We discuss the characteristics and quality of the recently developed Chinese SARS models, in particular with respect to their potential use in decision support. We aim to identify strengths and weaknesses in the Chinese modelling experience and thereby hope to facilitate more international collaboration.

Mathematical models of infectious disease in china

We searched all Chinese publications about mathematical models of infectious disease from 1994–2006 through the Chinese CAJ full-text database. CAJ is the Chinese internet library (since 1994) and includes nearly all scientific Chinese journals, including those on medicine, biology and mathematics. We used the key words 'model', 'modelling', 'mathematical' and 'disease' (in Chinese) to be mentioned somewhere in the whole paper. Then from these papers we selected those actually reporting mathematical modelling studies, i.e., not those advocating or referring to it. We classified the papers according to the type of disease: SARS, other infectious diseases and papers that were about infectious diseases in general, i.e. not disease specific.

Figure 1 displays the annual number of Chinese papers on infectious diseases that used modelling over the period 1994–2006. The total number of papers was 375. Large changes have taken place since 2003, the year of the SARS epidemic. Before 2003, the number of publications used to be 12–20 annually, since 2003 it rose four to fivefold, largely due to 64 papers on SARS-modelling published in the Chinese literature so far. However, the numbers of infectious diseases modelling papers that are not disease-specific and of papers on modelling of other infectious diseases have also been increasing.

China has an existing but modest tradition in modelling infectious diseases. Clearly, the SARS epidemic has resulted in an enormous boost to this scientific discipline, leading to disproportional large numbers of papers on SARS models,

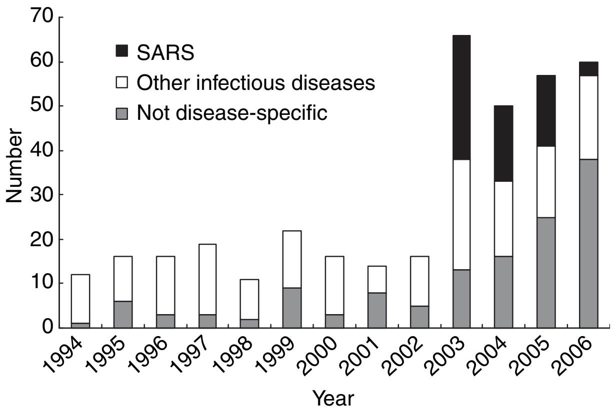

Figure 1 Annual number of Chinese peer-reviewed publications on modelling of infectious diseases over the period 1994–2006, distinguished into papers on SARS, other infectious diseases, and not disease-specific papers.

equalling the annual production of modelling papers in the years before the outbreak. Perhaps surprisingly, this overall extension of the research field has not lead to a decrease in the number of modelling papers on other infectious diseases, as may have been expected if there were a temporary shift of focus from 'normal' diseases to SARS-related diseases. Quite the contrary, their numbers have increased as well. The year 2006 has even resulted in the one-but-highest production of modelling-papers, even though there were only three papers on SARS-modelling.

Table 1 presents of the characteristics of Chinese articles about modelling of infectious diseases published in the Chinese literature from 1994–2006, divided into three time periods. In the table, only articles that are about a specific disease have been included. For the most recent period (2003–2006), the values were given separately for papers on SARS models and models for other infectious diseases.

It is clear that curve fitting was by far the most commonly applied technique all along from 1994 till now. Compartmental modelling was second, and its use has substantially increased after 2003. For every time period one of both types of techniques was applied in at least 80% of the modelling papers. Individual-based modelling was almost exclusively applied from 2003 onwards, and not only for SARS models. For the SARS modelling, relatively often more complex techniques were used, e.g. individual-based modelling, spatio-temporal models and other types (Autoregressive Integrated Moving Average (ARIMA) modelling and small-world network models). Spatio-temporal models were largely confined to application on SARS.

The main focuses of the modelling papers did not change much over time, but studying mathematical features of epidemics only became important after 2003, for models

Table 1 Overview of the characteristics of Chinese articles about modelling of infectious diseases published in the Chinese literature from 1994–2006, divided into three time periods

	1994–1997	1998–2002	2003–2006 Non-SARS	2003–2006 SARS
Number of articles	50	52	75	64
Type of model/model use:				
Curving fitting	46 (92)	45 (86)	53 (71)	32 (50)
Compartmental models	3 (6)	4 (8)	12 (16)	17 (27)
Individual-based models	0 (0)	1 (2)	8 (11)	3 (5)
Spatio-temporal models	1 (2)	2 (4)	1 (1)	8‡ (12)
Other types†	0 (0)	0 (0)	1 (1)	4 (6)
Main focus of the article:				
Understanding observed epidemiological trends	42 (84)	42 (81)	55 (73)	37 (58)
Prediction of future epidemiological trends	6 (12)	4 (8)	6 (8)	13 (20)
Prediction of effect of interventions	2 (4)	5 (10)	6 (8)	7 (11)
Mathematical features of epidemics	0 (0)	1 (2)	8 (11)	7 (11)

Only articles that are about a specific disease have been included. Values represent number of articles, with percentages (%) between parentheses.
†Other types of models include ARIMA models and 'small-world' network models: i.e. one paper on 'small-world' network model in not SARS group of 2003–2006, and three papers on ARIMA models and one paper on 'small-world' network model in SARS group of 2003–2006.
‡In spatio-temporal types, there are two real models to describe the SARS transmission, the other six papers only use spatio-temporal knowledge to describe the transmission but not give the real model. SARS, severe acute respiratory syndrome.

on SARS as well as on other infectious diseases. Half of the papers focused on the understanding of observed epidemiological trends, maybe as a consequence of limited expertise of using predictive techniques. Studying future trends was relatively often applied for SARS models.

Clearly, the SARS epidemic has led to a boost in modelling initiatives, which included an increase in more sophisticated techniques as well. However, it was quite surprising that not a single non-SARS related modelling paper after 2003 referred to any (Chinese or international) SARS modelling paper (not shown). Furthermore, out of the 64 Chinese modelling papers on SARS, the number of references to non-Chinese modelling papers was also modest: the important papers by Lipsitch *et al.* (2003) and Riley *et al.* (2003) were cited 12 and 13 times only, respectively (not shown). Apparently, many Chinese researchers have limited access to international literature or insufficient knowledge of the English language to use such papers.

Chinese models on SARS

Table 2 describes the characteristics of a selection of 17 models on the epidemiology and control of SARS published in the Chinese literature. These models were reported in 20 of the 64 publications (see previous section) on Chinese SARS models thus far. In the table we have presented all models that were sufficiently detailed in describing the mechanisms of SARS spread and its control, to allow the authors to predict epidemiological trends and the impact of different types of interventions beyond the observations the models were based on. They concern six deterministic and eight stochastic compartmental models based on various variants of the standard SIR approach, and one so-called 'small-world' network model using individual-based simulation. Moreover, we have included the two spatio-temporal models based on geographic information systems (GIS): i.e. a so-called 'Fly dots' model of SARS spread between geographical locations in China, and a spatio-temporal model linking SARS hotspots in Beijing to their geographical location. The remaining models (reported in 43 papers) used rather simple to very sophisticated curve-fitting methods, such as the ARIMA time-series methods (Ding *et al.* 2003), that basically described the observed patterns in SARS cases in order to make short-term extrapolations and/or to assess the impact of interventions actually applied. Three of the Chinese SARS models were reported in papers submitted when the epidemic was still ongoing but rapidly decreasing (i.e. May 2003) (Lin *et al.* 2003 Xia & Wu 2003; Xia *et al.* 2003), seven were

Table 2 Overview of some SARS models published in the Chinese literature in order of time of submission

Study (date of submission)	Population	Model design and technique	Focus	Caveats	Conclusions
Xia *et al.* 2003 (13 May 2003) Xia & Wu 2003 (May 2003)	Guangdong Hong Kong	Compartmental model	To analyse the pattern and predict the course of the SARS epidemic	Using statistical methods to calculate latent periods and other parameters. Using limited SARS data in Guangdong for simulation. Consider an infected and recovered two-compartment population	The simulation fitted the actual epidemic trend in Hong Kong very well. The model predicted that the epidemics in Guangdong and Hong Kong would be controlled by the middle of May 2003
Lin *et al.* 2003 (22 May 2003)	Beijing	Small world network model	To simulate the dynamics of the SARS epidemic. To evaluate the effect of starting providing transparency on the SARS epidemic to the public	Using limited SARS data of Beijing for simulation. Simulations of relatively small populations are translated to the scale of Beijing	Human contact rate and time from onset of symptoms to isolation are key factors to predict SARS infection. The public's response to more transparency about the SARS epidemic has caused sustained reduction in the number of infected cases
Gong *et al.* 2003 (2 June 2003)	Beijing	System dynamic model	To quantitatively analyse the importance of various control measures against SARS	Using limited SARS data of Beijing for simulation. Relatively arbitrary set of parameters and initial values	Reducing the onset-to-hospitalisation interval and effective quarantine are two key factors in controlling the transmission of SARS
Yang *et al.* 2003a (3 June 2003) Chen *et al.* 2003 (3 June 2003)	Beijing	Compartmental model	To estimate parameter values by various methods. To analyse the trend and to predict the course of the SARS epidemic	Lack of help from medical experts. The definitions of parameters are rather imprecise	The model predicted that the epidemic will peak after 60 days and be controlled after 123 days after taking the control measures timely
Yang *et al.* 2003b (5 June 2003)	No particular city	Compartmental model ('Fly dots' spreading model)	To describe the SARS epidemic in spatial-temporal dimensions	Assuming that people travelling in buses/trains do not infect others outside along the way. No validation of the model by SARS data	Jumped spread of SARS between two points over a long distance is affected by population distribution. SARS can spread through buses/trains along transportation lines
Wu *et al.* 2003 (6 June 2003) Chen *et al.* 2004 (13 August 2003)	Beijing Guangdong	Compartmental model (Susceptible, Exposed, Infectious, Recovered (SEIR) model)	To estimate the basic reproductive rate R_0. To assess the impact of control measures. To study the mechanisms of super-spreading events	Using limited SARS data of Beijing and Guangdong for simulation	R_0 is estimated at about 3.5. Inevitable high contact rates among families, hospital and public transport are the source of super-spreading events
Shi 2003 (9 June 2003)	Vietnam	Stochastic compartmental model	To mimic the SARS epidemic by Monte Carlo simulation	Using limited SARS data for simulation. Lack of help from epidemiologists	Monte Carlo simulation showed that super-spreading events played an important role in the spread of SARS

Table 2 (*Continued*)

Study (date of submission)	Population	Model design and technique	Focus	Caveats	Conclusions
Fang *et al*. 2003 (30 June 2003)	Beijing	Compartmental model	To simulate the SARS transmission in Beijing. To predict the number of probable SARS cases and deaths in a Beijing hospital by time series and Bayes method	Using limited SARS data for simulation. It is only suitable for predicting SARS epidemics in the short term. Classifies the population into only two groups, suspected of infection and infected	The model describes the SARS transmission better in the period of spread than in the period of control
Shi, Xu & Shui 2004 (29 October 2003)	Beijing	Compartmental model	To simulate and evaluate the effects of prevention and control measures in SARS transmission	Using limited SARS data for simulation. Lack of input from epidemiologists	The model contains a parameter 'anti-epidemic factor' to quantify the effects of isolation measures. A theoretical method to calculate its value from 0–1 was created by using Fuzzy mathematics
Zeng, Cheng & Huang 2004 (November 2003)	Beijing	Stochastic compartmental model	To define the relationship between control methods and their effectiveness	Using limited SARS data for simulation. Lack of input from epidemiologists	The timing and intensity of an intervention are key factors of the effectiveness of SARS control
Han, Wang & Liu 2004 (29 January 2004)	Beijing Hong Kong	Deterministic compartmental model (SIR model)	To estimate critical parameters (e.g. peak period, proportion hospitalised, re-infection rate.) To analyse parameters of the SARS transmission	Lack of the detailed data for simulating the SARS epidemic	The model showed that the overall duration of the SARS epidemic is about 5 months. The model predicted that the maximum number of hospitalised patients in Beijing would be about 2050
Liu *et al*. 2004 (5 April 2004)	Hong Kong Canada Singapore	Compartmental model	To assess the impact of control measures	Using limited SARS data for simulation	There is a distinct difference in the pattern of the epidemic before and after taking control measures. Control measures carried out in Hong Kong, Canada and Singapore (such as isolation) were effective
Wang *et al*. 2005 (29 July 2004)	Beijing	Multi-distribution and spatial analysis	To analyse the multi-dimensional (time and spatial) nature of SARS transmission	Difficult to introduce the spatial dimension to the modelling calculations	Revealed the spatial characteristics of the SARS epidemic in Beijing. Environmental factors such as adjoining districts, population density and number of medical staff are important in the prevention and control of SARS

Table 2 (*Continued*)

Study (date of submission)	Population	Model design and technique	Focus	Caveats	Conclusions
Cai *et al.* 2005 (25 August 2004)	Beijing	Compartmental model	To illustrate the model's ability to quantitatively evaluate intervention measures	The model was based on the assumption that the cases were infected with SARS-CoV and another unknown virus. This assumption has not been proved up to now	The study estimated the role of health care workers and the general population in the SARS epidemic. The control measures that were taken around 20 April 2003, played a key role in the control of the SARS epidemic in Beijing.
Xu *et al.* 2005 (8 September 2004)	Different locations within and outside China	Compartmental model (SEIR model)	To identify the values of critical parameters and their importance for the SARS epidemic	Lack of help from epidemiologists	Model explorations resulted in wide variety of values for R_0, ranging from 2.8 in Singapore to 21.9 in Inner Mongolia. Values for Hong Kong, Canada, Taiwan, Beijing, Shanxi, and Hebei were in between.
Zeng *et al.* 2005 (4 November 2004)	Beijing	Compartmental model	To determine key variables in the control of the SARS epidemic. To analyse the effectiveness of the so-called 'screening for fever' practice during epidemics	No validation with actual SARS data	The time from onset of symptoms to hospitalisation, the average number of contacts, the infection rate, and the rate of isolation were the key variables during the SARS epidemic. Based on the applied disease control measures and plans, the health system in Beijing can control the SARS epidemic rapidly
Yang 2006 (9 January 2006)	No particular city	Deterministic compartmental model (SIR model)	To estimate the values of key parameters in the SARS epidemic	Using limited SARS data for validation of the model. Lack of help from epidemiologists	The model provided a good fit of the data by simulating four distinct stages in the epidemic: increasing, controlled, steady and decreasing. It is very important for controlling SARS spread to take intervention measures timely

SARS, severe acute respiratory syndrome; SIR model, standard susceptible-infected model.

submitted at the very end of the epidemic (June) (Chen *et al.* 2003; Fang *et al.* 2003; Gong *et al.* 2003; Shi 2003; Wu *et al.* 2003; Yang *et al.* 2003a,b), and the remaining seven only after the epidemic. As a result, all papers only appeared in the literature after the SARS epidemic had ended.

All models aimed at describing the pattern of the SARS epidemic in a particular city. Most of the times this was Beijing (Cai *et al.* 2005; Chen *et al.* 2003, 2004; Fang *et al.* 2003; Gong *et al.* 2003; Han *et al.* 2004; Lin *et al.* 2003; Shi *et al.* 2004; Wang *et al.* 2005; Wu *et al.* 2003; Xia & Wu 2003; Xia *et al.* 2003; Xu *et al.* 2005; Yang *et al.* 2003a; b; Zeng *et al.* 2004, 2005), but some focused on cities in other provinces such as Guangdong (Wu *et al.* 2003; Xia & Wu 2003; Xia *et al.* 2003; Yang *et al.* 2003b; Chen *et al.* 2004), Shanxi (Xu *et al.* 2005), Hebei (Xu *et al.* 2005), Inner Mongolia (Xu *et al.* 2005) and Hong Kong (Xia & Wu 2003; Xia *et al.* 2003; Yang *et al.* 2003b; Liu *et al.* 2004). Probably because of lack of Chinese data, three models used data about foreign cities such as Hanoi, Vietnam (Shi 2003), Toronto, Canada (Liu *et al.* 2004) and Singapore (Liu *et al.* 2004), of which data was available through the internet. However, none of them actually drew conclusions that also had relevance for the Chinese situation. Some, especially the spatio-temporal models, focused on the details of one particular situation, which could be a real situation such as the city of Beijing (Yang *et al.* 2003b; Wang *et al.* 2005) or a theoretical situation (Gong *et al.* 2003). None of the models focused on the epidemic pattern of mainland China as a whole.

Three of the 17 compartmental models aimed to estimate the value of R_0 (Wu *et al.* 2003; Chen *et al.* 2004; Liu *et al.* 2004). Two models arrived at a value of 3.5, and one resulted in a range of 3.5–4.5. These values are similar to that found by Lipsitch *et al.* (2003) and Riley *et al.* (2003), which were published before the Chinese studies. Five models basically aimed at reproducing observed epidemic patterns in order to identify the key parameters in the spread of SARS and draw inferences about the best interventions. There was little consistency in their findings. Two models concluded that the onset-to-hospitalisation interval was the most important factor (Gong *et al.* 2003; Zeng *et al.* 2005), whereas one found that the contact rate was the key parameter (Han *et al.* 2004). Furthermore, one study concluded that effective quarantine and constant control was essential in the dynamics of SARS (Zeng *et al.* 2004), and another one the time-dependent infection rate (Shi 2003). Almost all models concluded that isolation of patients was the most important means to control SARS (Gong *et al.* 2003; Shi 2003; Shi *et al.* 2004; Wu *et al.* 2003; Chen *et al.* 2004; Han *et al.* 2004; Liu *et al.* 2004; Zeng *et al.* 2004, 2005; Yang 2006). However, two studies concluded that shortening the period from onset to hospitalisation by improving case-finding would be equally important (Gong *et al.* 2003; Zeng *et al.* 2005). Two other studies reported that decreasing the importation of cases would be the main intervention (Wu *et al.* 2003; Chen *et al.* 2004), and six models found that quarantine of close-contacts of cases combined with disinfection of the living-environment of cases is most effective (Shi 2003; Han *et al.* 2004; Liu *et al.* 2004; Shi *et al.* 2004; Zeng *et al.* 2004; Yang 2006).

It is clear that the Chinese modelling initiatives have had limited implications for policy advice about the SARS epidemic itself, simply because the reports were only available in the scientific literature after the epidemic. Also, as far as we can conclude from the papers, no modelling initiative had a direct link with decision makers before publication. However, from these papers policy makers may have learned how models can support their decision-making, so that there may be more interaction in case of re-emergence of SARS or an outbreak of another infectious disease.

Most of the 17 SARS models we investigated were based on very limited data or even no data at all. This is unsurprising, given the limited accessibility of data at the time of the epidemic. Also, the Chinese reporting system on infectious diseases (until 16 May, 2003) led to fragmented data sources, incomplete recording, and considerable delay in reporting. Therefore, most modellers had to resort to using WHO internet reports on the number of cases as a function of time of onset. More detailed epidemiological data, such as on the duration between onset and hospitalisation, proportions of infections in hospital settings, and numbers of close contacts in quarantine, were not available. As a consequence, essential parameters in the models were largely based on assumptions (Cai *et al.* 2005; Zeng *et al.* 2005), sometimes expressing very little knowledge about infectious disease in general (Chen *et al.* 2003; Yang *et al.* 2003a). This problem may have been overcome by involvement of experts in infectious disease control, but this often did not happen (Gong *et al.* 2003; Yang *et al.* 2003b; Wang *et al.* 2005). In fact, these and other modelling initiatives (including most of the curve-fitting studies) purely focused on mathematical issues and did not really consider practical implications with public health relevance.

Conclusions

Our overview of the recent Chinese literature on mathematical modelling of infectious diseases demonstrated a big increase in the number of publications after the SARS outbreak in 2003, not only on SARS itself but also on other infectious diseases. Although most Chinese SARS models were based on curve-fitting methods for the observed patterns of SARS cases over time, 17 modelling initiatives applied methods more applicable for decision-support in policy making, such as compartmental models. This number of modelling initiatives is of the same order of magnitude as what has been published in the international literature during the first years after the SARS epidemic (Bauch *et al.* 2005).

The Chinese researchers on infectious diseases modelling still have to overcome several limitations. The modelling studies were reported (and often also conducted) later than some important international studies, and the knowledge on SARS and sometimes even infectious diseases in general was often very limited among the study groups. After the SARS epidemic and based on the papers published, Chinese policy makers may now have obtained more knowledge about what modelling can do for them, such as predicting future trends of epidemics and offering advice about effective control options. Still, detailed high-quality data on infectious diseases must become more readily available to modellers. An important first step is the establishment of a special department for collecting data on infectious diseases in China. The establishment of a nationwide surveillance data collection system is already under way. Still, further harmonisation between the department of data collection and modelling groups will be necessary. On the other hand, new Chinese modelling studies on outbreaks of infectious diseases can take advantage of the SARS modelling experiences and the increased understanding of infectious diseases epidemiology and control. Also, it is good news that officials have realised that effective control of infectious diseases depends on multifield collaboration between public health, medicine, epidemiology, and mathematics. Perhaps the most important benefit of the Chinese SARS modelling efforts is not preparation for possible re-emergence of SARS, but rather preparation any future outbreak of infectious diseases.

We conclude that Chinese modellers would benefit from more collaboration with the international scientific community. The difficulty with reporting in the English language literature has considerably hampered demonstrating their experiences. We therefore hope that our overview of Chinese modelling initiatives will also facilitate more international collaboration. Researchers who would like to contact authors of papers listed in our review can obtain their contact addresses from the first and the corresponding author of this article.

Acknowledgments

This study was supported by the Commission of the European Community under the Sixth Framework Program Specific Targeted Research Project, SARS Control 'Effective and Acceptable Strategies for the Control of SARS and new emerging infections in China and Europe' (Contract No. SP22-CT-2004-003824). We are grateful for the discussions with the staff of the Department of Epidemiology, Beijing Institute of Microbiology and Epidemiology. In particular, we thank W.J. Zhao, L. Yan, H. Yang and S. Sheng for their critical review and comments.

Conflicts of interest

The authors have declared no conflicts of interest.

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