This is an electronic appendix to the paper by Gumel *et al*. 2004 Modeling strategies for controlling SARS outbreaks based on Toronto, Hong Kong, Singapore and Beijing experience. *Proc. R. Soc. Lond.* B **271**, 2223-2232. (DOI 10.1098/rspb.2004.2800.)

Electronic appendices are refereed with the text. However, no attempt is made to impose a uniform editorial style on the electronic appendices.

Electronic Appendix A: Interpretation of reproduction numbers ($\mathcal{R}_0, \mathcal{R}_c, \mathcal{R}^*$)

Each term of $\mathcal{R}_c$ (as given in Section 2.7) has an epidemiological interpretation. The mean duration in the asymptomatic class E is $1/D_1$ with contact rate $\epsilon_E\beta$, giving a contribution to $\mathcal{R}_c$ of $\epsilon_E\beta/D_1$. A fraction κ_1/D_1 goes from E to the symptomatic class I, with contact rate β and mean duration $1/D_2$, giving a contribution of $\beta\kappa_1/D_1D_2$. A fraction γ_1/D_1 goes from E to the quarantined class Q, with contact rate $\epsilon_Q\beta$ and mean duration $1/(\mu+\kappa_2)$, giving a contribution of $\epsilon_Q\beta\gamma_1/D_1(\mu+\kappa_2)$. A fraction $\kappa_1\gamma_2/D_1D_2$ goes from E to I to the isolated class J, with a contact rate of $\epsilon_J\beta$ and a mean duration of $1/D_3$, giving a contribution of $\epsilon_J\beta\kappa_1\gamma_2/D_1D_2D_3$. Finally, a fraction $\gamma_1\kappa_2/D_1(\mu+\kappa_2)$ goes from E to Q to J with a contact rate of $\epsilon_J\beta$ and a mean duration of D_3 giving a contribution of $\epsilon_J\beta\gamma_1\kappa_2/D_1D_3(\mu+\kappa_2)$. The sum of these individual contributions gives $\mathcal{R}_c$.

The two reproduction numbers $\mathcal{R}_0$ and $\mathcal{R}_c$ give the expected number of secondary cases produced by an index case. There is also a time-dependent *effective reproduction number* $\mathcal{R}^*$ which continues to track the expected number of secondary infections caused by each infective as the epidemic continues with control measures (quarantine of asymptomatic individuals and isolation of symptomatic individuals) in place. It is not difficult to show that if the inflow into the population from travellers and new births is small (i.e., if the epidemiological time scale is much faster than the demographic time scale), our model implies that $\mathcal{R}^*$ will become and remain less than unity, so that the epidemic will always pass. Even if $\mathcal{R}_c > 1$, the epidemic will abate eventually when the effective reproduction number becomes less than unity. For the model (1)-(6) with $p = 0$, the effective reproduction number is essentially

$$\mathcal{R}^* = \mathcal{R}_c \frac{S}{N} \ ,$$

but allows time-dependent parameter values as well.

In practice, control measures are implemented quickly and the number of infected individuals is small relative to the total population size, N. This implies S/N is approximately one and $\mathcal{R}^*$ is simply $\mathcal{R}_c$ with possibly time varying parameters. Thus, $\mathcal{R}_0$ determines whether there will be an outbreak, and $\mathcal{R}_c$ determines whether the control measures introduced when an outbreak is recognized will suffice to turn matters around right away. In our simulations we will assume that the parameters γ_1 and γ_2 are zero initially but are changed instantaneously to positive values when control measures are instituted, as an approximation to continuous increases to new values over a short time interval.

However, it should be remembered that if the epidemic takes so long to pass that there are enough new births and travellers to keep $\mathcal{R}^* > 1$, there will be an endemic equilibrium, meaning that the disease will establish itself and remain in the population.

If $p > 0$, there is no disease-free equilibrium. Consequently, there is at least one endemic equilibrium with a positive number of SARS-infected components. In this case, strictly speaking, the reproduction numbers are not defined.

Electronic Appendix B: Estimation of model parameters

The associated parameters of the model are estimated using currently available data, as is now described. Note that we focus on values for GTA and make comments when values are different for other locations.

Recruitment rate (Π) **and natural death rate**(μ)

The parameter Π models the daily net in-flow of people into the region. This accounts for birth, immigration and emigration, tourism etc. For a city such as Toronto, an estimate of $\Pi = 136$ people *per* day is plausible. Health Canada (Health Canada 2003a) reported an estimated 5-10 travel-related SARS infections for the entire country. Consequently, it is prudent to calculate p based on the recruitment of six infected individuals over the course of the first 100 days of the epidemic. Thus, $p = 0.0004424$. The analytic theory developed for the reproduction numbers ($\mathcal{R}_0$, $\mathcal{R}_c$ and $\mathcal{R}^*$) depends on the existence of a disease-free equilibrium, which requires $p = 0$. However, we use $p > 0$ in the simulations. The parameter p is small and was observed to have little effect on the simulation results (see Figure 4a). Although not done in this study, both time-dependent and stochastic recruitment rates could be used for the simulations. The parameter p could also be interpreted as the rate of animal-to-human transmission of SARS.

The natural death term (μ) represents the per capita rate at which individuals die of causes other than SARS. This is typically obtained from the expression $\frac{1}{\mu}$ = life expectancy. Using a life-expectancy of 80 years, it follows that $\mu = 0.000034$ *per* day. The parameter μ would be different for the different locations to which we apply the model, but is sufficiently small that its variation can be ignored. In the absence of disease, the steady-state population is $\Pi/\mu = 4$ million for $\Pi = 136$ people and $\mu = 0.000034$ *per* day. Estimates for Π and p for the other three SARS-affected regions are given in the caption to Figure 2.

Rate of development of clinical symptoms (κ_1, κ_2)

These parameters measure the rate at which asymptomatic and quarantined individuals develop clinical symptoms (and transfer to the symptomatic class). The estimated median time for self-reported earliest known exposure to onset of symptoms in GTA ranges from 6 days to 9 days (Booth et al. 2003). A study of SARS epidemiology in Hong Kong (Donnelly et al. 2003) estimated the mean incubation period to be 6.4 days. Taking all these into account, it is reasonable to assume that the parameters κ_1, κ_2 lie in the interval $0.1 \leq \kappa_1 < \kappa_2 \leq 0.167$. For simulation purposes, we choose $\kappa_1 = 0.1, \kappa_2 = 0.125$ *per* day.

Recovery and mortality rates ($\sigma_1,\ \sigma_2, d_1, d_2$)

It is conceivable, due to the strength of their immune systems, that some symptomatic SARS-infected individuals recover from the disease prior to their hospitalization and subsequent isolation. We model the rate at which symptomatic individuals recover using the parameter σ_1. Furthermore, σ_2 is used to model the recovery rate of isolated individuals. The parameters d_1 and d_2 model, respectively, the rates at which symptomatic and isolated individuals die because of SARS. Since the symptomatic individuals are not treated prior to isolation, it is assumed that the death rate of symptomatic individuals is higher than that of isolated individuals ($d_1 > d_2$). The four

parameters considered here are estimated as follows: suppose the case mortality is X and the expected time until recovery or death (or expected time in isolation) is T. Then, the SARS-induced mortality, d, is defined by $d = (1 - \mu T)X/T$ and $\sigma = (1 - \mu T)(1 - X)/T$ (as *per* (Day 2002)). The WHO (2003a) estimated the SARS-induced fatality to be between $15\% - 19\%$. Assuming that symptomatic individuals are not treated prior to isolation ($d_1 > d_2$), we set $X_1 = 0.19$ and $X_2 = 0.15$. Furthermore, recent data suggests that isolated individuals typically stay in hospitals (or in isolation) for a period of 10 to 22 days, it is appropriate to choose $T_1 = 24$ and $T_2 = 22$. Using these values of X_1, X_2, T_1 and T_2 in the expressions for d and σ gives $\sigma_1 = 0.0337$, $\sigma_2 = 0.0386$, $d_1 = 0.0079$ and $d_2 = 0.0068$ *per* day. It should be noted that the case mortality rate is age-dependent. While the mortality rate in people younger than 64 is estimated to be between $15\% - 19\%$, the rate rises to 50% or higher (Booth et al. 2003; Donnelly et al. 2003) in people older than 64. Although not considered here, it would be instructive to incorporate age-dependent mortality in models of SARS epidemiology. It should also be noted that the case fatality rate calculated from the Beijing data used here is markedly different from that for other regions (case fatality for Beijing is approximately 7%; see Wang & Ruan 2003). As a result, we used a lower set of parameter estimates when running simulations for Beijing. In particular, we use $X_1 = 0.11$, $X_2 = 0.09$ and $T_1 = 22$, $T_2 = 21$ giving $\sigma_1 = 0.0413$, $\sigma_2 = 0.0431$, $d_1 = 0.0055$ and $d_2 = 0.0041$.

Quarantine rate (γ_1) and isolation rate (γ_2)

The parameters γ_1 and γ_2 model the rate of quarantining asymptomatic and isolating symptomatic individuals respectively. The asymptomatic individuals are assumed to be identified through the use of contact tracing. Quarantined individuals are assumed to be at home receiving partly-effective treatment. Owing to SARS morbidity, symptomatic individuals are likely to seek medical attention and therefore be placed in isolation. Since detecting symptomatic individuals seem easier than detecting asymptomatic individuals, it is reasonable to assume that $\gamma_2 \geq \gamma_1$.

During the initial stages of the epidemic, we take $\gamma_1 = \gamma_2 = 0$. At some point, health officials recognized the epidemic and began to implement quarantine and isolation procedures. These control measures were refined and enhanced over time, leading to a gradual improvement in their effectiveness. This could be modeled using continuous, time-varying parameter values for γ_1 and γ_2, but little data is available to guide a choice for the form of these functions. Consequently, we approximate this situation by supposing that both γ_1 and γ_2 are step functions in time, switching from $\gamma_1 = \gamma_2 = 0$ to some other constant value at a particular date. We take the post-switch values to be $\gamma_1 = 0.1$ *per* day and $\gamma_2 = 0.5$ *per* day. These choices reflect the fact that SARS-infected individuals likely remained in the community for a relatively long period of time (10 days) before quarantine, and in fact many were not quarantined before developing symptoms. We take the date at which the switch occurs to be March 30, 2003. In reality, quite effective control measures were probably put into place at least as early as mid-March, but given we are using a step function as an approximation for their implementation, choosing a slightly later starting date is warranted.

Transmission coefficients ($\beta, \epsilon_E\beta, \epsilon_Q\beta, \epsilon_J\beta$)

Contact between a susceptible and an infected individual is associated with a risk of infection. The transmission coefficients β, $\epsilon_E\beta, \epsilon_Q\beta$ and $\epsilon_J\beta$ measure the infectiousness and contact rate associated with the interaction between a susceptible and a SARS-infected individual in the symptomatic, asymptomatic, quarantined, and isolated classes, respectively. Currently there are

insufficient data to estimate these parameters, and therefore we were forced to make some simplifying assumptions. It should be stressed, however, that the quantitative outcome of this study is strongly affected by these parameters.

Although SARS is known to be transmitted primarily by symptomatic patients, infrequent asymptomatic transmission has not been ruled out. The latter may indeed have triggered the second outbreak in GTA (Health Canada 2003a). Asymptomatic transmission may be possible due to the failure of a few individuals with weakened immune systems to elicit detectible clinical symptoms such as fever and cough. This possibility is included in the model through the modification factors ϵ_E and ϵ_Q associated with the asymptomatic transmission of SARS. Although, for simplicity, the parameters ϵ_Q and ϵ_E will be set to zero in all the numerical simulations of this study (Section 3), these parameters are retained in the model formulation and mathematical analysis components of the paper. It should be emphasized that qualitatively similar numerical results are obtained when employing a small value for these asymptomatic transmission coefficients.

The modification parameter ϵ_J reflects the level of hygienic precautions during isolation. If these measures were perfect, then ϵ_J would be zero, resulting in no further SARS infections from isolated individuals. Health Canada data shows that isolated individuals were responsible for most infections in Canada (Health Canada 2003a), suggesting that the transmission coefficient, $\epsilon_J\beta$, associated with this class was larger before stringent hygienic measures were put in place. This is, primarily, due to two reasons. One is the lack of adequate knowledge of modes of SARS transmission during the early stages of the epidemic. The second is the fact that, at the early stage of the epidemic (prior to the implementation of stringent hygienic measures in isolation), care givers (e.g., family members or health care workers) attending to isolated individuals tend to have frequent and very close contact with the isolated individuals, resulting in numerous cases of nosocomial infections.

Once it was recognized that in-hospital transmission of infection was common, stricter hygienic control measures, including use of negative pressure rooms for patients, and N95 face masks, gloves, and gowns for medical personnel, were adopted. To include this important component of the transmission process in our model, we assume that ϵ_J was positive for some period of time until the inadequacy of the isolation measures was recognized, at which point we suppose that ϵ_J then becomes zero. For the GTA, for instance, we take the date at which ϵ_J becomes zero to be 3 weeks after the initiation of isolation and quarantine (i.e., April 20, 2003). Again, it would be more realistic to take ϵ_J as a continuously decreasing function of time (reflecting gradual improvements in hygienic precautions), but we approximate this as a step function. We used a 3 week lag between the onset of control measures (isolation and quarantine) and the improvement of hygienic precautions to reflect the fact that 1-2 weeks would elapse before the care givers of initially quarantined or isolated individuals would display symptoms, and some period of time after that would be required before health care officials could coordinate stricter hygienic precautions in isolation.

The two parameters that remain to be specified are the transmission rate coefficient, β, and the value of the modification parameter, ϵ_J, before it switches to zero on April 20, 2003. Both parameters were chosen to produce model predictions that best matched the data on cumulative deaths over time for each of the four regions. Specifically, we chose the values of these parameters that yielded the smallest sum-of-squared-deviations (SSD) of the models predictions for cumulative deaths from the data, over the total time period for which data were available.