

the cell cortex is a rate-limiting step for force generator function. Given that cortically localized $G\alpha_i$ and Pins also dictate spindle positioning in *Drosophila* (10), we propose that modulation of cortical $G\alpha$ signaling to generate defined pulling forces on astral microtubules is a conserved mechanism to translate polarity cues into appropriate spindle positioning.

References and Notes

- J. A. Knoblich, *Nature Rev. Mol. Cell Biol.* **2**, 11 (2001).
- P. Gönczy, *Trends Cell Biol.* **12**, 332 (2002).
- J. Pellettieri, G. Seydoux, *Science* **298**, 1946 (2002).
- K. J. Kempthues, J. R. Priess, D. G. Morton, N. Cheng, *Cell* **52**, 311 (1988).
- S. W. Grill, P. Gönczy, E. H. Stelzer, A. A. Hyman, *Nature* **409**, 630 (2001).
- M. Gotta, J. Ahringer, *Nature Cell Biol.* **3**, 297 (2001).
- F. Yu, X. Morin, Y. Cai, X. Yang, W. Chia, *Cell* **100**, 399 (2000).
- M. Schaefer, A. Shevchenko, J. A. Knoblich, *Curr. Biol.* **10**, 353 (2000).
- M. Schaefer, M. Petronczki, D. Dorner, M. Forte, J. A. Knoblich, *Cell* **107**, 183 (2001).
- Y. Cai, F. Yu, S. Lin, W. Chia, X. Yang, *Cell* **112**, 51 (2003).
- P. Gönczy *et al.*, *Nature* **408**, 331 (2000).
- Examination of the genome sequence and sequencing of full-length cDNAs revealed that *gpr-1* (WormBase code F22B7.13) and *gpr-2* (C38C10.4) are both expressed and that they result from a recent gene duplication event. We found a single *gpr* homolog in the available *C. briggsae* genome (CBG10100), whose inactivation caused a phenotype indistinguishable from that observed in *C. elegans*.
- B. Zhang *et al.*, *Nature* **390**, 477 (1997).
- K. Colombo, P. Gönczy, unpublished data.
- B. Etemad-Moghadam, S. Guo, K. J. Kempthues, *Cell* **83**, 743 (1995).
- L. Boyd, S. Guo, D. Levitan, D. T. Stinchcomb, K. J. Kempthues, *Development* **122**, 3075 (1996).
- S. Guo, K. J. Kempthues, *Cell* **81**, 611 (1995).
- T. J. Hung, K. J. Kempthues, *Development* **126**, 127 (1999).
- S. Strome, W. B. Wood, *Cell* **35**, 15 (1983).
- K. J. Reese, M. A. Dunn, J. A. Waddle, G. Seydoux, *Mol. Cell* **6**, 445 (2000).
- L. De Vries *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 14364 (2000).
- R. J. Kimple *et al.*, *J. Biol. Chem.* **276**, 29275 (2001).
- M. Natochin, K. G. Gasimov, N. O. Artemyev, *Biochemistry* **40**, 5322 (2001).
- See supporting online material.
- Average peak velocities in $\mu\text{m/s}$ ($\pm\text{SEM}$ at the 0.95 confidence interval) were as follows (A, anterior spindle pole; P, posterior spindle pole): *gpr-1/2(RNAi)*, A: 0.20 ± 0.03 , P: 0.18 ± 0.04 , $n = 15$; *goa-1/gpa-16(RNAi)*, A: 0.21 ± 0.04 , P: 0.22 ± 0.03 , $n = 15$; *par-3(it71) gpr-1/2(RNAi)*, A: 0.18 ± 0.04 , P: 0.18 ± 0.03 , $n = 13$. Values for *par-3(it71)* were A: 0.89 ± 0.11 , P: 0.90 ± 0.07 , $n = 20$ (5).
- K. G. Miller, J. B. Rand, *Genetics* **156**, 1649 (2000).
- M. F. Tsou, A. Hayashi, L. R. DeBella, G. McGrath, L. S. Rose, *Development* **129**, 4469 (2002).
- L. S. Rose, K. Kempthues, *Development* **125**, 1337 (1998).
- S. W. Grill, J. Howard, E. Schäffer, E. H. K. Stelzer, A. A. Hyman, unpublished data.
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Materials and Methods

Figs. S1 to S4

References

Movies S1 to S7

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Transmission Dynamics of the Etiological Agent of SARS in Hong Kong: Impact of Public Health Interventions

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We present an analysis of the first 10 weeks of the severe acute respiratory syndrome (SARS) epidemic in Hong Kong. The epidemic to date has been characterized by two large clusters—initiated by two separate “super-spread” events (SSEs)—and by ongoing community transmission. By fitting a stochastic model to data on 1512 cases, including these clusters, we show that the etiological agent of SARS is moderately transmissible. Excluding SSEs, we estimate that 2.7 secondary infections were generated per case on average at the start of the epidemic, with a substantial contribution from hospital transmission. Transmission rates fell during the epidemic, primarily as a result of reductions in population contact rates and improved hospital infection control, but also because of more rapid hospital attendance by symptomatic individuals. As a result, the epidemic is now in decline, although continued vigilance is necessary for this to be maintained. Restrictions on longer range population movement are shown to be a potentially useful additional control measure in some contexts. We estimate that most currently infected persons are now hospitalized, which highlights the importance of control of nosocomial transmission.

The evolution and spread of the etiological agent of severe acute respiratory syndrome (SARS), a novel coronavirus (1), has resulted in an unparalleled international effort coordinated by the World Health Organization (WHO) to characterize the virus, develop

diagnostic tests, and formulate optimal treatment protocols to reduce morbidity and mortality (2–4). Great progress has been made with, for example, the full sequence of the RNA virus reported on 13 April 2003 (5, 6). The epidemic apparently originated in early

November in the Guangdong province of the People’s Republic of China, and then spread rapidly throughout the world via air travel. As of 21 May 2003, 7956 cases have been reported to WHO from 28 countries, with 666 deaths recorded. The epidemics in Hong Kong, mainland China, Singapore, Taiwan, and Toronto (Canada) have been of particular concern because of the multiple generations of local transmission seen in those areas. The extent of these epidemics has been worsened by the occurrence of large clusters of infection linked to single individuals and/or spatial locations.

The rate of spread of an epidemic—and whether such spread is self-sustaining—depends on the magnitude of a key epidemiological parameter, the basic reproduction number (R_0), defined as the average number of secondary cases generated by one primary case in a susceptible population (7). After the introduction of an agent into a population, a

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related parameter—the effective reproduction number (R_t)—quantifies the number of infections caused by each new case occurring at time t . This value is typically lower than that of R_0 for two reasons: the effect of control measures in reducing transmission, and the depletion of susceptible individuals during the epidemic. For an epidemic to be controlled, R_t needs to be reduced below 1, the self-sustaining threshold. Estimation of reproduction numbers requires population heterogeneity to be accounted for—reflecting, for example, variation in infection risk with spatial location, variation in contact rates between groups, and between-case variability in infectiousness (7, 8).

Heterogeneity in R_t between cases appears to be particularly important for SARS because of the occurrence of “super-spread” events (SSEs)—rare events where, in a particular setting, an individual may generate many more than the average number of secondary cases. The Hong Kong epidemic to date has been characterized by two large clusters of cases, together with ongoing transmission to close contacts. In the first cluster, at least 125 people were infected on or soon

after 3 March 2003 in the Prince of Wales Hospital (PWH) by the index patient for the Hong Kong epidemic (2). In the second cluster, an unknown number of people were infected from a probable environmental source in the Amoy Gardens (AG) estate (Kwung Tong district). After mixing with fellow residents, families, and friends, more than 300 people became infected. Examination of local reports of SARS investigations (9) support the distinction between these two large SSEs and the other contact-based infections. It may be that the distinction between typical infection events and SSEs reflects the two different routes of transmission so far identified as likely for this virus—namely, respiratory exudates and fecal-oral contact (with contaminated surfaces also perhaps of importance in hospital and residency settings).

As it may be some time before these SSEs can be characterized in terms of transmission route, we adopt the usual epidemiological notation and define R_0^{XSS} to be the average number of infections caused by one typically infectious individual, excluding SSEs, in an entirely susceptible population. Similarly, R_t^{XSS} is the average number of infections,

excluding SSEs, caused by individuals in later generations at time t . The long-term fate of the outbreak (containment, growth, or endemic persistence) will therefore ultimately depend on both the extent of typical transmission (and how this is modified by controls) and the relative frequency and magnitude of SSEs. These two factors contribute additively to the overall reproduction number R_t :

$$R_t = R_t^{XSS} + p^{SSE}N^{SSE} \quad (1)$$

where p^{SSE} is the probability that any infection leads to an SSE, and N^{SSE} is the average number infected during an SSE. Because little is currently known about how to influence either p^{SSE} or N^{SSE} , reducing R_t^{XSS} should be the key aim in any early public health intervention strategy. We therefore focus on estimating R_t^{XSS} for the outbreak of SARS in Hong Kong and on evaluating the effectiveness of different interventions in reducing transmission.

We estimate R_t^{XSS} for the SARS epidemic in Hong Kong by fitting a detailed mathematical transmission model to spatially stratified incidence time series derived from the clinical records of the 1512 cases reported by 6 May 2003 (10). The possible effects of asymptomatic (and thus unreported) cases were not analyzed in the current study because of insufficient population serological survey data with which to estimate infection levels. Three epidemiological parameters determine the reproduction number:

$$R_t^{XSS} = \beta TS \quad (2)$$

where β is the transmission coefficient (incorporating infectiousness and contact rate), T is the infectiousness-weighted duration of infection, and S is a factor representing the effect of geographic heterogeneity and susceptible depletion on disease spread (11). All three factors are likely to change as an epidemic progresses and control measures are introduced. This expression illustrates how controls can limit transmission: by reducing local contact rates (affecting β), by shortening the delay between onset of symptoms and hospitalization (affecting T), by improving the effectiveness of isolation measures in hospitals (also affecting T), and by imposing restrictions on longer range movements/contacts (affecting S).

However, a coherent estimation framework requires the use of a more sophisticated dynamical model to capture the nonlinearity and spatial locality of transmission and to incorporate information on how key parameters (e.g., incubation period, time from exposure to first appearance of clinical symptoms of infection, and T) vary between individuals. Capturing the duration and temporal evolution of infectiousness within the infected patient is critical. Data are limited, but circumstantial evidence based on contact tracing

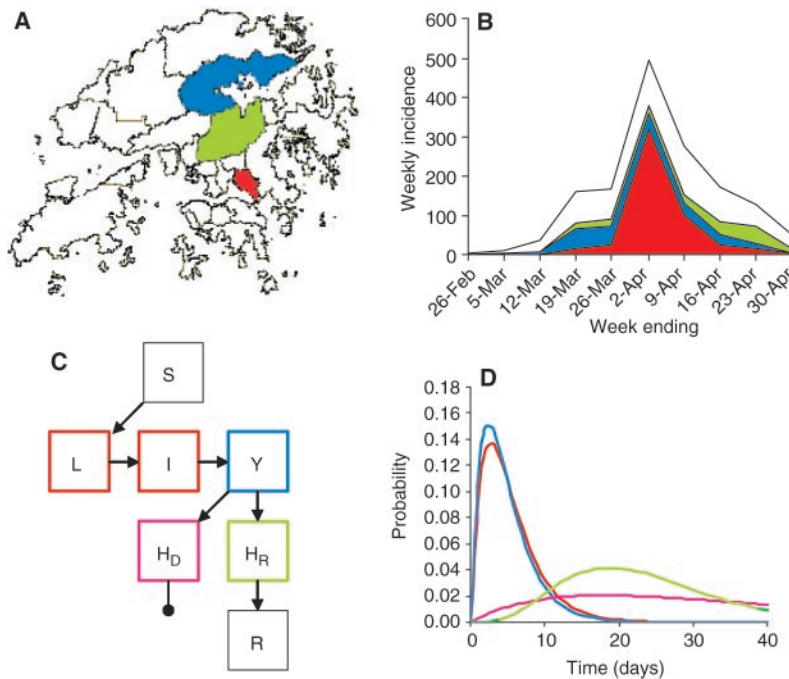


Fig. 1. Input data and model structure. (A) Map of Hong Kong showing the location of each district used in the model. More than 70% of cases reported through 16 April 2003 are from the three colored districts: Kwung Tong (red), Tai Po (green), and Sha Tin (blue). (B) Weekly incidence (by time of hospital admission) with the color coding used in (A). (C) Schematic flow diagram of transmission model used. Each district in the metapopulation model uses the structure shown. Susceptible individuals (S) become infected and enter a latent class (L). They then progress to a short asymptomatic and potentially infectious stage, I (see text), before the onset of symptoms and progression to class Y. It is assumed that every infected individual eventually enters hospital and either recovers (H_R) or dies (H_D). Color code: red, incubation period; blue, time from symptoms to hospitalization; magenta, time from hospitalization to death; green, time from hospitalization to recovery. (D) Distributions [of gamma form; see (10)] for the waiting times of the compartments of the stochastic model shown in (C). Colors match those used in (C). Distributions shown are estimates for the start of the epidemic. The onset-to-hospitalization distribution changes during the epidemic as a result of more rapid hospital admission.

tentatively suggests that infectiousness coincides with, but does not precede, clinical symptoms (3). Additionally, the large number of SARS cases reported to have resulted from hospital exposure (about 200 cases in addition to the PWH cluster) suggests that infectiousness does not wane substantially for some time after symptoms become apparent—a conclusion reinforced by the temporal evolution of patients' viral loads (12).

Choice of a suitable model framework is not straightforward; a variety of approaches are possible, ranging from a simple deterministic compartmental approach to a spatially explicit, individual-based simulation. Given the data available for Hong Kong, we base our analyses on a stochastic metapopulation compartmental model. A metapopulation approach is appropriate because the incidence of SARS has varied substantially by geographical district (Fig. 1, A and B). A stochastic model is required because chance fluctuations in case numbers can be large in the early stages of an epidemic. Stochastic models predict both average trends and variability, so that a more robust assessment can be made of what changes are likely to be caused by chance and what changes genuinely reflect process and the impact of interventions.

We classify the population of each district into susceptible, latent, infectious, hospitalized, recovered, and dead individuals (Fig. 1C). Epidemiological coupling between districts is assumed to depend on their adjacency (Fig. 1A) (11). Incubating and infectious categories are further divided into multiple stages, chosen in number and duration so as to match accurately the estimated delay distributions determining disease progression and diagnosis (Fig. 1D) (10). Multiple realizations of the stochastic model are required both for parameter estimation and to generate predicted case incidence time series.

The mean time from the onset of symptoms until hospital admission and subsequent isolation of suspect SARS cases has decreased significantly over the course of the epidemic to date (Fig. 1D) (10). Changes in the onset-to-hospitalization distribution were treated as an input to the model. Other potential factors, such as time variation in the rate or nature of close contact between individuals, could also affect R_t^{XSS} . The impact of these can be captured by allowing the underlying coefficient of transmission, β , to vary through time. For simplicity, we assume β could have taken different values during each of three equally spaced time periods over the epidemic observed to date.

We assume that infectiousness begins just before the onset of symptoms and remains constant during the symptomatic phase. We assigned the relative infectiousness of hospitalized patients to match the overall rate of within-hospital transmission for the epidemic to date. Simulations are

seeded explicitly with the PWH cluster, given its importance in determining the later pattern of the Hong Kong epidemic. Detailed contact tracing identified 125 first-generation cases in this cluster. However, it is also important to account for the fact that the index patient arrived in Hong Kong more than a week before admission to PWH, during which time he infected multiple individuals. It is not possible to gain a precise estimate of the number of SARS infections occurring before 3 March 2003 (the index patient's admission date to PWH), but examination of the case data stratified by onset and admission date indicate this number to be definitely less than 110 and most likely in the 60–70 range. We therefore include within the seeding infection event the first 70 cases admitted to hospital that were not traced to the PWH cluster (11)—giving a total of 195 infections assumed to occur on 3 March.

Model fit [see (11) for full list of estimated parameters] to the case-incidence data was qualitatively good, in terms of capturing both the temporal development of overall incidence (Fig. 2A) and the pattern of spatial spread (Fig. 2B). We estimate the initial value of the reproduction number, R_0^{XSS} , in Hong Kong to have been 2.7 [95% confidence interval (CI), 2.2 to 3.7]. Therefore, even in the absence of SSEs, the virus was capable of inducing an epidemic from the first introduced case. To reproduce the approximately 20% of cases known from contact tracing to have hospital-related exposure, hospital transmission must constitute about 50% of the value of R_0^{XSS} , the discrepancy being a result of the time delay between infections generated before and after admission as well as the extreme nonlinearity of the epidemic curve. We estimate that patients in hospital transmit infection at about 20% of the rate of symptomatic patients in the community—reflecting the effectiveness of isolation procedures and perhaps lowered infectiousness once recovery starts. However, this lowered rate of transmission is counterbalanced by the longer time spent in hospital relative to the time spent symptomatic in the community before hospitalization.

If the seeding is assumed to include only the 125 contacts traced to the PWH index patient rather than the 195 total early infections assumed for the baseline scenario, the estimated value of R_0^{XSS} increases to 3.4, but the quality of model fit is decreased very significantly ($P < 0.001$). If 35 (half of the 70 assumed in the baseline scenario) extra non-contact-traced cases are included in the seeding event, R_0^{XSS} is estimated to be 2.8 with a comparable quality of fit to the baseline scenario. This variation in R_0^{XSS} estimates associated with the assumed seed size reflects the fact that pre-

cise attribution of early infections into SSE and non-SSE categories is problematic; by assuming a larger initial seed size, we increase the size of the SSE caused by the PWH index case, and hence decrease estimates of the level of non-SSE transmission required to reproduce the observed epidemic.

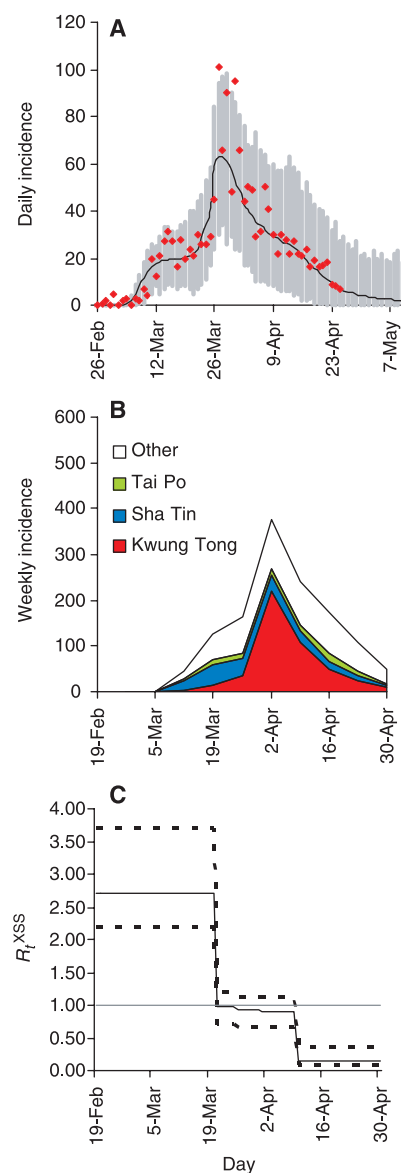


Fig. 2. (A) Estimated reproduction number in the absence of SSEs, R_t^{XSS} , for the period of the epidemic for which data are available. Confidence intervals are also shown. The self-sustaining threshold $R_t^{XSS} = 1$ is shown as a solid line. (B) Model estimates of weekly case incidence (average of 1000 model realizations) for the three districts with the most cases, by date of hospital admission (to be compared with Fig. 1B). (C) Model estimate of case incidence (average of 1000 model realizations) at the best-fit parameter set with 95% prediction intervals). Prediction intervals are generated from extreme realizations at the boundaries of the multivariate confidence intervals. The upper and lower bounds of the data are also shown.

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Despite this uncertainty, R_0^{XSS} values in the range 2.2 to 3.7 represent low to moderate transmissibility; hence, the early rapid growth in case numbers observed reflects the chance occurrence of the PWH SSE (without which it is arguable that the Hong Kong outbreak would never have reached epidemic proportions). An important conclusion emerges from this estimate of R_0^{XSS} : Epidemic control will be easier to achieve than for other viral infectious agents such as influenza (13) or measles (7) with higher R_0 values.

We estimate the Amoy Gardens (AG) SSE to have occurred on 19 March (95% CI, 18 March to 20 March) and to have infected 331 (95% CI, 295 to 331) people. Although the model was constrained to allow only a single SSE after the initial seeding of the PWH SSE, it is encouraging that the timing of the event is consistent with independent investigations into that cluster of cases. It is thought that the sewage system became infected when the brother of a resident of AG used a toilet there on either 14 or 19 March (14).

We determined that current data do not permit reliable estimation of the level of infectiousness during the period just before symptom onset. A better understanding of how infectiousness varies during disease pathogenesis—such as that which might be gained from detailed contact-tracing studies or quantitative assessment of viral shedding through time (12)—would clearly benefit disease control planning. However, to date, indications are that most transmission occurs late in infection, which clearly facilitates infection control.

Our analysis gives insight into the effect of different control measures on transmission, as quantified by R_t^{XSS} (Fig. 2C). The mean time from symptom onset to hospital admission fell to 79% of its original value by 26 March (a reduction of 1 day on average) and to 76% of its original value by 1 April, giving rise to 9% and 11% drops in transmission, respectively (10, 11). Changes in the transmission coefficient were even more significant, with β estimated to have dropped to 37% of its original value by 12 March and to 6% of its original value by 1 April. Reductions in β are most easily attributed to increased awareness of the infection, 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 effect. Overall, the reductions in onset-to-hospitalization time, population contact rate, and hospital transmission are estimated to have caused the reproduction number, R_t^{XSS} , to drop to 1.0 (95% CI, 0.7 to 1.2) by 21 March, to 0.9 (95% CI, 0.6 to 1.1) by 26 March, and to 0.14 (95% CI, 0.09 to 0.35) by 10 April (Fig. 2C).

The Hong Kong epidemic has been characterized by substantial levels of transmission occurring in hospitals (Fig. 3A). Contact tracing indicates that more than 22% of cases were associated with hospital-related exposure. In part this reflects the SSE that occurred in the Prince of Wales hospital. Nonetheless, if we exclude the Amoy Gardens outbreak, then 19% of all cases subsequent to the PWH cluster are still linked to hospital exposure. Figure 3B shows how well the model reproduces the separate case time series for the PWH and Amoy clusters and cases arising from hospital and non-hospital-based exposure, and Fig. 3C illustrates the good fit between observed and estimated hospital occupancy levels. Figure 3C also shows that as a result of the long period spent by SARS patients in hospital, the total prevalence of hospitalized SARS patients inevitably becomes much higher than the commu-

nity prevalence after new admission rates start to decline, reinforcing the need for effective hospital infection control measures even in the latter stages of the epidemic.

These results indicate that R_t^{XSS} is now below the self-sustaining threshold of 1 in Hong Kong, and thus that the epidemic is currently under control—in the sense that infection rates are declining. They also suggest that reductions in population contact rates (both in the community and in hospitals) played the predominant role in achieving control. However, more rapid hospitalization also provided an important additional effect. It should also be noted that these estimates assume constant infectiousness from the onset of symptoms up to the time of hospitalization; if infectiousness increases after symptom onset, the effect of the observed 1-day reduction in onset-to-hospitalization times could have been substantially greater, reducing R_t^{XSS} by up to 34% (11). However, even in this

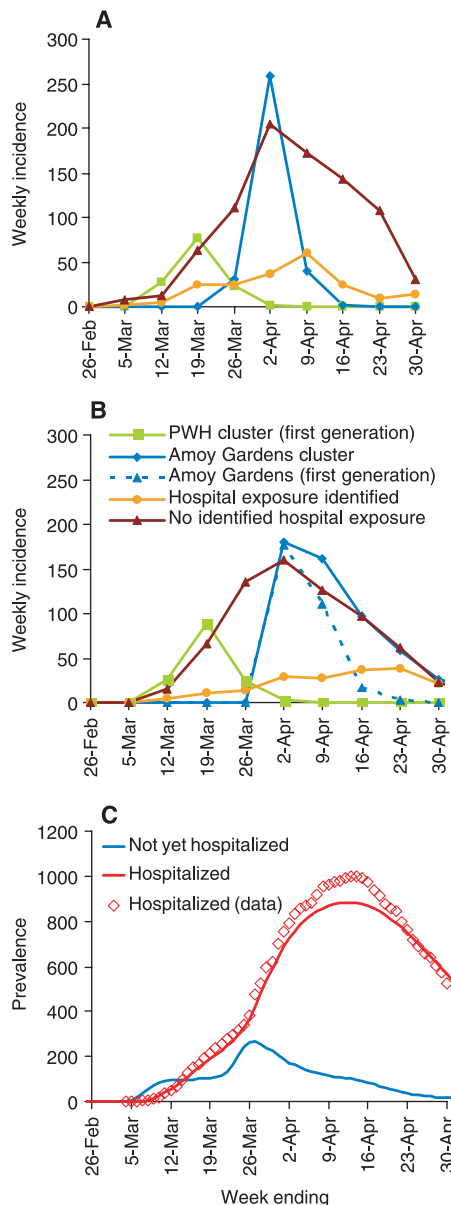


Fig. 3. (A) Weekly admissions stratified by SSE cluster or type of exposure, as determined by contact tracing: 125 cases (green line) were attributed to direct exposure to the Hong Kong index patient on or shortly after his admission to the Prince of Wales Hospital on 3 March 2003 [only first-generation cases are shown (11)]; 331 cases (blue line) were attributed to the Amoy Gardens outbreak. Of the remaining 1056 cases, 201 were attributed to exposure occurring in a hospital or clinic (purple line) and 855 were attributed to other exposures or had no contact tracing available (ochre line). (B) Best fit model predictions stratified by exposure, matching definitions in (A). The predicted Amoy Gardens case time series has been further stratified into first-generation cases only (dashed line) and first-generation plus all additional cases (solid line). The correspondence between the data and model predictions for Amoy Gardens suggests that only first-generation cases were successfully linked to the Amoy cluster by contact tracing. The narrow width of the observed Amoy cluster peak shown in (A) suggests that cases in this cluster had a narrower onset-to-hospitalization distribution than other cases. Comparing model predictions and data for hospital exposure-related cases also indicates that hospital transmission has decreased faster in recent weeks than is captured by the model. (C) Best fit model predictions for the total prevalence of symptomatic SARS patients, stratified according to whether they have been hospitalized.

case, we estimate contact rate reductions and hospital infection control to have been key in achieving control of transmission.

The structure of the model also allows us to investigate the effect of contact patterns between districts on disease transmission [as quantified by S in the expression for R_t given above (11)]. The contact rate of an individual with the population from a contiguous district relative to that from the same district was estimated as 0.57 (95% CI, 0.42 to 1.0). However, the contact rate between noncontiguous districts was much lower, at 0.02 (95% CI, 0 to 0.10) relative to the within-district contact rate. Hence, transmission appears to be highly geographically localized, offering further options for control. Given that the most populous districts are highly connected, these estimates of between-district mixing suggest that restricting movement could have a substantial impact on net transmission. A complete ban on travel between districts is estimated to have the potential to reduce R_t^{XSS} by 76%. Beyond Hong Kong, this suggests that movement restrictions might represent a useful control measure in circumstances where it was not possible to reduce the average

onset-to-hospitalization time substantially—for example, in resource-poor countries or if a number of SSEs occurred in close succession and hospital capacity was temporarily exceeded.

A key advantage of transmission modeling is that alternative control scenarios can be examined, giving insight into the potential effectiveness of different intervention strategies. Figure 4 shows five such scenarios, simulated with parameters estimated for the earliest stages of the Hong Kong epidemic. The scenario of no control measures is shown to give rise to a catastrophic epidemic, even in the absence of SSEs. Figure 4 also illustrates that although reductions in onset-to-hospitalization times comparable to those achieved in Hong Kong can achieve some reduction in transmission, on their own they are insufficient to control SARS; other measures are also needed (such as improved infection control in hospitals, voluntary reductions in population contact rates, or movement restrictions).

Given the R_0^{XSS} estimate of 2.7, our analyses suggest that the etiological agent of SARS is moderately rather than highly transmissible, except in the very specific settings that have induced the two major clusters to date. The epidemic in Hong Kong appears to have moved through three phases: early exponential growth, a plateau period with daily case numbers fluctuating around 50, and (from May onward) a phase of declining incidence with daily case numbers below 20. The low value of R_t^{XSS} in the latter phase in part reflects the considerable changes in human behavior within Hong Kong that have taken place during the epidemic. Individuals have been mixing, traveling, and socializing less in public areas, such as restaurants or sports venues. Isolation measures in affected hospitals have been improved. As the epidemic wanes and the public perception of risk changes, there is a danger that increased mixing could act to trigger a resurgence in case numbers, with R_t^{XSS} again exceeding 1. Moreover, because of the slow rate of clinical progression to recovery or death (on the order of 1 month), most infected people in a decaying epidemic will be found in hospitals, so that hospital control measures should be enforced rigorously. Continued vigilance is necessary during the decay phase of the epidemic, with reinforcement of public health messages, to ensure eradication of this infection from Hong Kong.

Ensuring as rapid a decline of the epidemic as possible is also important to minimize the probability that another SSE might occur, given that the frequency of SSEs is likely to be related to infection prevalence. Epidemic decay is guaranteed only where R_t is maintained below 1, which ultimately depends not just on controlling regular transmission events (i.e., maintaining $R_t^{XSS} < 1$) but also on understanding and controlling SSEs. Given our current estimates of $R_t^{XSS} = 0.14$ and

an SSE event size of $N^{SSE} \approx 250$, epidemic growth driven by SSEs would occur only if more than 1 in 300 infections were to generate new SSEs (i.e., $p^{SSE} N^{SSE} > 0.86$ from Eq. 1). Given current controls in Hong Kong and the current tally of two documented SSEs from more than 1500 infections, this outcome appears unlikely. However, without a much better understanding of the causes of the extreme between-case heterogeneity in secondary infection rates for SARS, it is impossible to exclude the possibility that a much higher frequency of SSE-based transmission might be seen in other countries and/or contexts. In the context of Hong Kong, our analysis shows that further reducing the mean time from onset of symptoms to hospital admission by a day or so would speed eradication if contact rates remain low, and would ensure continued control of the epidemic even in the face of moderate increases in population contact rates. Therefore, every effort to promote more rapid admission and subsequent isolation of suspect SARS cases should continue to be made. The availability of specific and sensitive virological diagnostic tests will help in this task.

The reported cases to date in Hong Kong and elsewhere may simply reflect people with the most severe clinical symptoms of infection with the new SARS virus. Our estimates of case reproductive numbers are based on reported SARS cases only. If additional asymptomatic infections in the community were not diagnosed, reproduction number estimates based on all infections may differ depending on the frequency of asymptomatic cases, whether this frequency varied during the epidemic, and the extent to which such cases can transmit infection. Community-based serological surveys will therefore be valuable to assess past infection levels and should be a priority once a specific and sensitive serological test is available.

Worldwide, the virus appears to have been contained in most developed countries. Dangers still persist, however, in populous regions of the world with a limited public health infrastructure and poor disease-reporting systems. The situation in mainland China remains severe, with high case numbers reported daily. The Chinese government recently introduced more draconian measures designed to restrict mixing and travel (15). The current analysis provides some optimism that such methods might be successful at limiting further spread, although it remains too early to judge whether they will be sufficient to bring the epidemic under control. One of the key lessons from recent events in Hong Kong has been the importance of good-quality data capture systems to permit detailed epidemiological analyses day by day, to inform both health policy formulation and the evaluation of intervention impact.

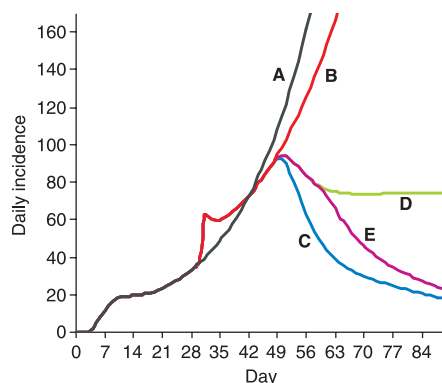


Fig. 4. Effect of alternative control scenarios on progression of a hypothetical epidemic with Hong Kong-like characteristics. No SSEs other than an initial seeding event of 50 infections on day 0 are modeled. Five scenarios are shown: (A) No control measures or change in population behavior, giving rise to a catastrophic epidemic. (B) No change in behavior but a reduction in mean onset-to-hospitalization time of 2 days achieved on day 30, the effect of which is to temporarily increase admission numbers but to reduce transmission by 19%. (C) As B, but with complete cessation of movement between districts imposed on day 45 (the effect of which is to reduce transmission by 76%). These control measures are seen to be sufficient to control the epidemic even in the absence of population behavior change. (D) As B, but with a 50% drop in population contact rates and hospital infections from day 45—just sufficient to prevent epidemic growth. (E) As D, but with a 70% reduction in hospital transmission from day 55—sufficient to rapidly control the epidemic. For all scenarios, Hong Kong demographic parameters were used and averages of 1000 model realizations are shown.

References and Notes

1. J. S. Peiris *et al.*, *Lancet* **361**, 1319 (2003).
2. N. Lee *et al.*, *N. Engl. J. Med.* **348**, 1986 (2003).
3. S. M. Poutanen *et al.*, *N. Engl. J. Med.* **348**, 1995 (2003).
4. T. G. Ksiazek *et al.*, *N. Engl. J. Med.* **348**, 1953 (2003).
5. Michael Smith Genome Sciences Centre (www.bcgsc.ca/bioinfo/SARS).
6. M. A. Marra *et al.*, *Science* **300**, 1399 (2003); published online 1 May 2003 (10.1126/science.1085953).
7. R. M. Anderson, R. M. May, *Infectious Diseases of Humans: Dynamics and Control* (Oxford Univ. Press, Oxford, 1991).
8. O. Diekmann, J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation* (Wiley, New York, 2002).
9. Hong Kong Police Department, *Selection of Daily Reports of SARS Cases* (unpublished).
10. C. A. Donnelly *et al.*, *Lancet*, published online 7 May 2003 (<http://image.thelancet.com/extras/03art4453web.pdf>).
11. See supporting data on Science Online.
12. J. S. M. Peiris *et al.*, *Lancet*, published online 9 May 2003 (<http://image.thelancet.com/extras/03art4432web.pdf>).
13. N. M. Ferguson, S. Mallett, H. Jackson, N. Roberts, P. Ward, *J. Antimicrob. Chemother.* **51**, 977 (2003).
14. *Outbreak of Severe Acute Respiratory Syndrome (SARS) at Amoy Gardens, Kowloon Bay, Hong Kong, Main Findings of the Investigation* (Hong Kong Department of Health, 2003).
15. World Health Organization, Communicable Disease Surveillance & Response (www.who.int/csr/sars/guidelines/en).
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Transmission Dynamics and Control of Severe Acute Respiratory Syndrome

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Severe acute respiratory syndrome (SARS) is a recently described illness of humans that has spread widely over the past 6 months. With the use of detailed epidemiologic data from Singapore and epidemic curves from other settings, we estimated the reproductive number for SARS in the absence of interventions and in the presence of control efforts. We estimate that a single infectious case of SARS will infect about three secondary cases in a population that has not yet instituted control measures. Public-health efforts to reduce transmission are expected to have a substantial impact on reducing the size of the epidemic.

SARS is a recently described illness of humans with a high case-fatality rate (*I*) that has spread widely since November 2002. Probable cases have been reported in 31 countries, with extensive ongoing transmission in Taiwan and China, continuing transmission in Hong Kong, and major outbreaks that are now under control in Singapore (Fig. 1A) and Vietnam (2). The causative agent of SARS appears to be a novel coronavirus (3–5).

We have used mathematical models of SARS transmission to estimate the infectiousness of SARS from the rate of increase of cases,

to assess the likelihood of an outbreak when a case is introduced into a susceptible population, and to draw preliminary conclusions about the impact of control measures.

The basic reproductive number of an infection, R_0 , is defined as the expected number of secondary infectious cases generated by an average infectious case in an entirely susceptible population. This quantity determines the potential for an infectious agent to start an outbreak, the extent of transmission in the absence of control measures, and the ability of control measures to reduce spread. R_0 can be expressed as $R_0 = kbD$, where k is the number of contacts each infectious individual has per unit time, b is the probability of transmission per contact between an infectious case and a susceptible person, and D is the mean duration of infectiousness. In contrast to R_0 , the effective reproductive number, R , measures the number of secondary cases generated by an infectious case once an epidemic is underway. In the absence of control measures, $R = R_0x$, where x is the proportion of the population susceptible. During the course of an epidemic, R declines because of the depletion of susceptibles in the population and the implementation of specific

control measures. To stop an outbreak, R must be maintained below 1.

We analyzed data on the first 205 probable cases of SARS reported in Singapore to obtain relevant epidemiologic parameters (6). The number of secondary SARS cases per index case was highly variable (Fig. 1B) in each week but fell from a mean of 7 for index cases with symptom onset in the first week of the Singapore outbreak to a mean of 1.6 in the second week to a mean below 1 in most weeks thereafter (Fig. 1B) ($P < .04$, Cuzick test for trend). This decline in secondary cases coincided with the application of control measures, including isolation of SARS cases and quarantine of their asymptomatic contacts. Enhanced surveillance of contacts for the development of symptoms resulted in a decline in the time from symptom onset until hospital isolation (Fig. 1C). Because control measures were rapidly applied, there are too few data from Singapore to provide a reliable estimate of R from the period before the institution of control measures.

We therefore used an alternate approach, estimating R from the rate of exponential growth in the number of cases in several other settings and with the use of data from Singapore on the mean serial interval, defined as the time from the onset of symptoms in an index case to the onset of symptoms in a subsequent case infected by the index patient (7). The mean serial interval (8) in Singapore was 8.4 days (SD = 3.8) (Fig. 1E), although, as expected, it was higher for episodes of transmission in which the index case had onset of symptoms in the first 2 weeks of the outbreak before full-scale interventions were in place (Fig. 1F; mean for first 2 weeks was 10.0 days; SD = 2.8 days).

With the use of these estimates, we estimated values of R on the basis of the number of cases that had been reported by a particular time, $Y(t)$, under four assumptions: (i) $Y(t) = 1358$ cases reported in Hong Kong on 19 April, $t = 63$ days after the first case on 15 February (2); (ii) $Y(t) = 425$ cases reported in Hong Kong on 28 March (2), just before the application of specific measures to control

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Transmission Dynamics of the Etiological Agent of SARS in Hong Kong: Impact of Public Health Interventions

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