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Modeling and public health emergency responses: Lessons from SARS

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ABSTRACT

Modelers published thoughtful articles after the 2003 SARS crisis, but had limited if any real-time impact on the global response and may even have inadvertently contributed to a lingering misunderstanding of the means by which the epidemic was controlled. The impact of any intervention depends on its efficiency as well as efficacy, and efficient isolation of infected individuals before they become symptomatic is difficult to imagine. Nonetheless, in exploring the possible impact of quarantine, the product of efficiency and efficacy was varied over the entire unit interval. Another mistake was repeatedly fitting otherwise appropriate gamma distributions to times to event regardless of whether they were stationary or not, particularly onset-isolation intervals whose progressive reduction evidently contributed to SARS control. By virtue of their unknown biology, newly-emerging diseases are more challenging than familiar human scourges. Influenza, for example, recurs annually and has been modeled more thoroughly than any other infectious disease. Moreover, models were integrated into preparedness exercises, during which working relationships were established that bore fruit during the 2009 A/H1N1 pandemic. To provide the most accurate and timely advice possible, especially about the possible impact of measures designed to control diseases caused by novel human pathogens, we must appreciate the value and difficulty of policy-oriented modeling. Effective communication of insights gleaned from modeling SARS will help to ensure that policymakers involve modelers in future outbreaks of newly-emerging infectious diseases. Accordingly, we illustrate the increasingly timely care-seeking by which, together with increasingly accurate diagnoses and effective isolation, SARS was controlled via heuristic arguments and descriptive analyses of familiar observations.

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Introduction

In the summer of 2008, at a field station high in the Canadian Rockies, a handful of public health physicians met with a larger number of infectious disease modelers to discuss the intersection of modeling and public health policymaking. This workshop arose from the observation that, while the infectious disease modeling community is comparatively small, it is contributing increasingly to the development of policy to address foreseeable public health problems. Until recently, however, our role in shaping actual responses to infectious disease outbreaks had been more limited.

Modelers published thoughtful articles after the 2003 severe acute respiratory syndrome (SARS) crisis (e.g., Anderson et al. 2004), but had limited, if any, real-time impact on the global response. The reason arguably is that we did not provide what health policymakers needed, reliable projections of the impact of alternative actions. By overestimating the potential of managing contacts versus cases, moreover, we may even have inadvertently contributed to a lingering misunderstanding of means by which this epidemic was controlled that will affect their future responses to newly-emerging infectious diseases.

Among its many uses, modeling can improve our understanding of actual pasts, as well as make predictions about hypothetical futures. In this spirit, we share reflections on our collective contribution to policymaking during the 2003 SARS epidemic that grew out of discussions at this retreat. While all participants shared a common goal – increasing the utility of modeling to public health decision makers – this essay is not their consensus about the best means of attaining that goal. Neither is it a thorough review of the SARS modeling literature. Most of us also supported policymaking during the more recent influenza pandemic, but SARS was so much more challenging that our earlier experience more fully exemplifies the value and difficulty of policy-oriented modeling.

When SARS emerged, US health policy decision-makers had only just begun involving modelers in their deliberations, convening working groups on smallpox and anthrax modeling in 2002 and 2003, respectively. And SARS was a new human disease. While the causal agent was identified quickly, experience with diseases caused by other coronaviruses was much less informative than the previous H1N1 and intervening pandemics and annual influenza were during

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2009. By virtue of their experience with influenza, moreover, modelers were invited to contribute to preparedness exercises during which relationships were forged that bore fruit during the actual pandemic.

The confidence in modeling that our assistance in preparing for and responding to this foreseeable crisis engendered may extend to routine public health policymaking. During unforeseen crises, however, the utility of modeling depends not only on more accurate and timely insights than we provided during the global response to SARS, but more effective communication. As observations are most familiar to policymakers, here we endeavor to support heuristic arguments about the contribution of various public health measures to SARS outbreak control by descriptive analyses of salient observations.

Lessons from SARS

Public health officials may have multiple mitigation options to consider in the face of emerging threats. During the 2009 influenza pandemic, for example, there were various pharmaceutical (vaccine, antiviral medications) and nonpharmaceutical (closing schools, staying home, or wearing masks) options. Because the efficacy of existing pharmaceuticals against newly-emerging infectious diseases generally is unknown, authorities cannot rely on them. They can, however, promulgate guidelines for managing patients or their contacts, and modelers should be able to inform their decisions.

Contact management

Early SARS models demonstrated the theoretical impact of isolation *before* symptom onset on disease transmission (e.g., Lipsitch et al. 2003; Fig. 6), and thus the potential benefit of interventions such as contact tracing and quarantine. Because the impact of any intervention depends not only on its efficacy, but on the proportion of targets reached, knowledgeable public health practitioners might have cautioned against overestimating the ease of identifying asymptomatic people in whom pathogens were replicating. Where published observations permit assessment, only about 5% of infected contacts of SARS patients (i.e., susceptible people associating with infectious ones intimately enough for infection) were in fact isolated before symptom onset. In Singapore, for example, only 11 of the 238 people ultimately diagnosed as probable cases (Tan 2005) and in Taiwan only 24 of 480 (Hsieh et al. 2005) had been quarantined. Other contacts were identified in Singapore, but evidently their perceived risk did not warrant movement restriction.

Could infected contacts have been identified more efficiently? In Beijing, 30,178 close contacts of 2,521 probable cases were quarantined over the course of the epidemic (Pang et al. 2003). Analysis of a subset of those individuals with good records (covering 2,195 contacts of 582 patients from 5 districts) revealed a range in the probability of diagnosed illness among quarantined individuals from 0% to 15.4%, depending on their relationship to the patient. Transmission was relatively high among spouses, other relatives, friends, and other household members, and low among co-workers, schoolmates, and healthcare workers. Separately, Ou et al. (2003) studied geographically representative precincts throughout Haidian District, where 1,210 contacts of 171 patients were quarantined. The probability of infection among a subset of 383 quarantined people ranged from 0% to 31.1%, also depending on the nature of their contact with patients. Consistent with the findings of Pang et al. (2003), caring for ill household members imposed the greatest risk, followed by visiting and residing in the same household. In sharp contrast to the situation in Hong Kong, where a faulty sewage system at the Amoy Gardens apartment complex may have facilitated fecal-oral transmission (Hong Kong DOH, 2003), no risk was associated with sharing an apartment building or workplace. In Singapore, 73.5% of cases were infected in healthcare institutions (overall, 49.3% were healthcare workers, 37.4% friends or visitors, and 13% other patients), 17.2% at home, and 3.4% in the community or workplace (Goh et al. 2006).

When infectious people infect less than one susceptible person on average, epidemics wane. Interventions to reduce the average number of secondary infections (typically denoted $\mathfrak{R}$) most expeditiously are preferable, provided all else (including, e.g., compliance and cost) is equal. The impact of such interventions depends crucially on pathogen life cycles and host contact patterns. Thus, in some environments, with some infectious agents, certain interventions may reduce disease transmission, whereas in other environments, or with other agents, the same interventions may not, despite being applied with equal diligence. As will be apparent, the natural history of SARS readily explains why encouraging people with compatible prodromal symptoms to seek care (and ensuring that clinicians and hospital infection control personnel had the wherewithal to diagnose and isolate them effectively) was only marginally less effective than quarantine. Because infected people are more easily identified when symptomatic, the greater efficiency of this intervention more than compensated for any deficit in its efficacy.

One can assess the potential impact of any intervention on a transmissible disease by calculating its effect on the reproduction number. The naming of this quantity reflects its demographic origin (Heesterbeek 2002), but infectious disease modelers focus instead on the average number of effective contacts while infectious, where *effective* means sufficiently intimate for infection of susceptible individuals; the consensus for SARS is roughly 3 (World Health Organization, 2003). Because $\mathfrak{R}=\mathfrak{R}_0(1-p)$, where $\mathfrak{R}_0$ is the basic reproduction number and p is the product of any intervention's efficiency and efficacy, we solve for the $\mathfrak{R}_0$ at which $\mathfrak{R}=1$, below which threshold outbreaks subside. With the aforementioned 5% efficiency observed in Singapore and Taiwan, and assuming 100% efficacy (i.e., quarantined people infected no one), evidently quarantine could not control any disease whose $\mathfrak{R}_0>1.05$. Thus, while implementing this measure may have communicated authorities' concern about the situation – possibly increasing compliance with recommended hand washing, mask wearing, and social distancing practices – evidently quarantine per se contributed little to SARS control.

Because contact management can be socially disruptive, potential costs and benefits must be weighed realistically. Identifying only 11 probable cases among 7,863 contacts restricted to their homes in Singapore and 47 among 4,331 telephoned daily (Tan 2005) imposed significant (if unquantified) costs, apparently for minimal gains. We have dates of symptom onset and isolation for clinically diagnosed cases in Singapore, but do not know which had been quarantined or telephoned daily, so cannot determine if identified contacts were isolated any more quickly than others, as Tan's (2006) juxtaposition of weekly proportions of probable cases who had been identified as contacts and mean onset-isolation intervals suggests. Similarly, in Taiwan, only 24 probable cases were identified by quarantining 55,632 contacts and none by quarantining 95,828 travelers from SARS-affected areas (Hsieh et al. 2005). We do not know how many probable cases were quarantined in Beijing, but the ratio of contacts to patients reported by Pang et al. (2003) was 12; in Taiwan, this factor was 116 (316 including travelers), and in Singapore, it was 33 (51 including those telephoned).

Tailoring activities to specific risk groups – those defined by Ou, Pang, and their co-workers, for example – could mitigate the social cost. In Beijing, quarantine was most appropriate for people who cared for ill household members. Being instructed to quickly seek medical care should any symptom that might herald SARS develop, however, was appropriate even for contacts with lower risk exposures. In Singapore, paradoxically, those telephoned actually were at much greater risk (47/4,331) than those quarantined (11/7,863). Case management also can be problematic. In Taiwan, for example, the incidence of laboratory-confirmed influenza was elevated among young adults hospitalized during 2003, with the excess presumably suspected of having SARS. The proportion of suspect cases not reclassified as probable – an overestimate absent consistent laboratory analyses – was nonetheless modest, relative to misclassification of uninfected people as contacts (in Singapore, e.g., 1–58/12,194 > 99.5% were misclassified), and most patients benefit from medical care.

Case management

If not by contact management, how was SARS controlled? Available evidence suggests that the reduction in time from symptom onset to clinical presentation and diagnosis during the course of this outbreak, together with increasingly effective isolation and other infection-control procedures, contributed most to containment.

This hypothesis also can be explored mathematically. Because $\mathfrak{R}_0$ is the sum (while infectious) of products of contact rates and probabilities of transmission on contact, either or both of which may vary with time since infection or symptom onset, in principle estimating the impact of isolating infected people at any time is straightforward. If we make the simplifying assumptions that probabilities of transmission on contact reflect infectiousness, which is proportional to viral load (successive logarithms of which can, in turn, be represented via a continuous statistical distribution), and that contact rates do not change substantially during illnesses, we can determine from the appropriate cumulative distribution function when isolation would have prevented $\mathfrak{R}_0 - 1$ infections.

Such an estimate can be derived from analyses of samples collected during the SARS epidemic. In the most exhaustive of several quantitative RT-PCR studies to date, He et al. (2007) analyzed 614 serological samples, 96 throat washes, and 224 fecal samples from SARS patients to determine viral loads at successive times after symptom onset. As the causal agent was transmitted primarily via respiratory secretions (except possibly among residents of the Amoy Gardens apartment complex), it seems prudent to base our estimate on results from the throat washes. Given the assumptions outlined above, together with a gamma distribution, these results suggest that for a disease with $\mathfrak{R}_0 = 3$, isolation that was 100% effective in blocking transmission could prevent $\mathfrak{R}_0 - 1$ infections (and thus lead to epidemic control) if implemented up to 5.2 days after symptom onset, on average (Fig. 1). The operational requirements can be calculated for any efficacy. For example, isolation that was only 80% effective should suffice to effect disease containment if implemented up to 4.4 days after symptom onset under the given assumptions, and so on. Analyses of the earlier studies of Peiris et al. (2003) and Cheng et al. (2004) yield similar results. That said, we must emphasize that these simple calculations are intended to be heuristic. If contact rates declined sharply after symptom onset, for example, the time available for isolation would be overestimated. Day et al. (2006), Fraser et al. (2004) and Lloyd-Smith et al. (2003) have developed frameworks for evaluating such questions more rigorously in future outbreaks of newly-emerging infectious diseases.

Figs. 2 and 3 illustrate daily mean intervals between symptom onset and diagnosis and proportions diagnosed within 4 days of symptom onset (i.e., during the largely noninfectious prodrome), respectively, by onset date in Singapore and Taiwan. The remarkable similarity of these observations in societies valuing different aspects of human nature suggests a common behavioral mechanism for the control progressively attained globally (Wallinga and Teunis 2004): As patients were not very infectious until acutely ill, evidently SARS was controlled by their earlier and probably progressively more effective isolation *after* symptom onset (Feng et al. 2009, Table 2), phenomena that authorities facilitated mainly (recall that only 58 of 238 probable cases in Singapore and 24/480 in Taiwan were traced) via effective health communications (Menon 2006) with healthcare providers as well as the general population (Chen et al. 2006). Others have noted that these times to event were not stationary (e.g., Anderson et al. 2004), which precludes fitting the otherwise appropriate gamma distribution (Donnelly et al. 2003, Riley et al. 2003), even by epoch (Leung et al. 2005).

It is safe to assume that shortening intervals between the onset of clinical symptoms and isolation of patients with communicable diseases will reduce their effective infectious periods and thus the extent of onward transmission. Could modelers have demonstrated that timely isolation – not quarantine – was the key to controlling SARS early enough to have influenced the public health response to this crisis (especially in light of the Amoy Gardens event, which may have biased responsible officials towards more aggressive interventions)? Feng et al. (2009) demonstrate that the ratios of infection rates during the prodrome and acute phases fitted to the first 30 days and all hospital admissions are similar, answering this question affirmatively. But could we have convinced health authorities to allocate more resources to encouraging people – especially those who might have been exposed to someone subsequently diagnosed – to seek medical care upon experiencing symptoms that might herald SARS, and to aiding clinicians in diagnosing, and infection control personnel in isolating patients? Also, looking ahead, as participants in the Canadian workshop endeavored to do, what lessons from SARS might increase the utility of modeling the next time that a new infectious disease emerges?

Applying the lessons

Evaluating models is difficult, especially in the throes of public health emergencies, but the disparate predicted and realized impacts

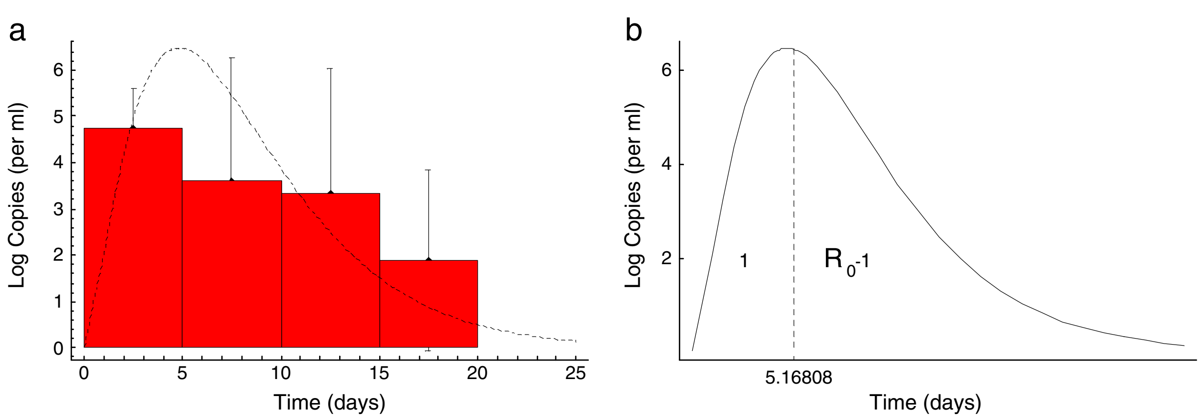

Fig. 1. a) Estimated viral load (log copies per ml) from quantitative RT-PCR on throat washings from SARS patients (means and 95% CI within 5-day intervals post-symptom onset), fitted gamma distribution ($\alpha = 2.49$, $\beta = 3.23$), and b) time post-symptom onset by which isolation that was 100% effective would prevent $\mathfrak{R}_0 - 1$ infections.

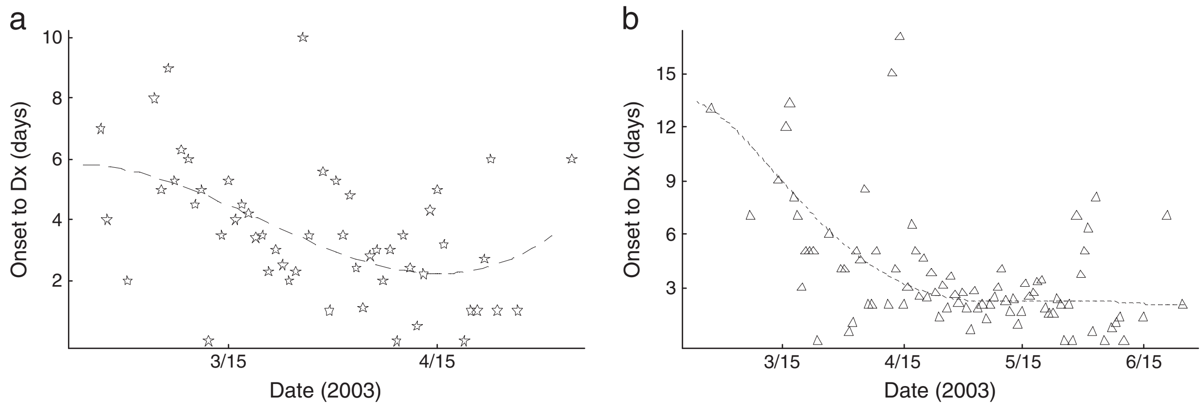

Fig. 2. a) Intervals from symptom onset to diagnosis and polynomial regressions, which account for temporal variation in daily numbers of persons at risk, by onset date in Singapore (stars) and b) Taiwan (triangles). While fifteen stars and twenty-six triangles represent single individuals, the mean quickly became less than that at which $\mathfrak{R}=1$.

of quarantine during the SARS epidemic reinforce the importance of such evaluations and the care with which they must be performed. Even the best modeling is limited by inaccurate or incomplete information. And during health crises, humanitarian needs trump record-keeping. Nonetheless, to ensure that interventions are modeled realistically, epidemiologists must scrutinize all available information lest observations that seem invaluable in hindsight be underappreciated or even overlooked. For example, Lipsitch et al. (2003; Fig. 1d) observed that the mean number of secondary infections per case in Singapore climbed dramatically when time from onset to isolation exceeded four days. To our knowledge, however, the implication of this observation vis-à-vis the potential impact of case versus contact management has not heretofore been articulated. Nonetheless, the inference that infected people were not particularly infectious until acutely ill was subsequently substantiated by the isolation of the SARS coronavirus and assessment of viral loads and shedding as functions of time from symptom onset. Shortening the period between such observations and deductions will ensure that timely public health decisions are based on credible science in future.

Influencing public policy

Once models have been evaluated and any deficiencies remedied, pertinent analytical or simulation results must be translated into actionable information for policy makers. Mathematicians may be convinced by the relative magnitude of partial derivatives of control reproduction numbers with respect to alternative parameters, but to have any impact whatsoever on decision making, such results must be expressed in the language of public health practice and with reference to readily available (or quickly improvisable) interventions. Until recently, few modelers had been intimately involved in emergency response or policy development, so facilitators with practical experience in these areas, who understood the potential of modeling in elucidating the relevant issues, were indispensable. Recent experiences may have narrowed the gap between the health and mathematical sciences, but field observations or results of natural experiments still carry more weight among most public health practitioners.

Modeling may guide or support observational studies. While the impact of closing schools and cancelling large public gatherings during future influenza pandemics was predicted by modeling (Ferguson et al. 2006, Germann et al. 2006), it may have been more persuasively communicated by analyses of actions taken by state and local policymakers in cities throughout the United States during the 1918 pandemic (Hatchett et al. 2007). By their own account, the epidemiologists who performed the latter study would not have known what patterns to seek in historical records without the guidance provided by modeling. But do the apparently beneficial effects of historical school closures reliably translate into similar contemporary effects, given secular changes in family and workforce structure? Even if contacts among schoolchildren could be reduced, any possible benefit might be offset by increased contacts between children and adults, some elderly (e.g., grandparents caring for children so that parents could continue working). And elderly people are more likely to die of complications.

Similarly, at a time when elected officials were deeply concerned about the threatened reintroduction of smallpox by terrorists and some modelers were arguing for the resumption of universal vaccination (e.g., Kaplan et al. 2002), most public health officials were persuaded that contact tracing, vaccination, and surveillance of

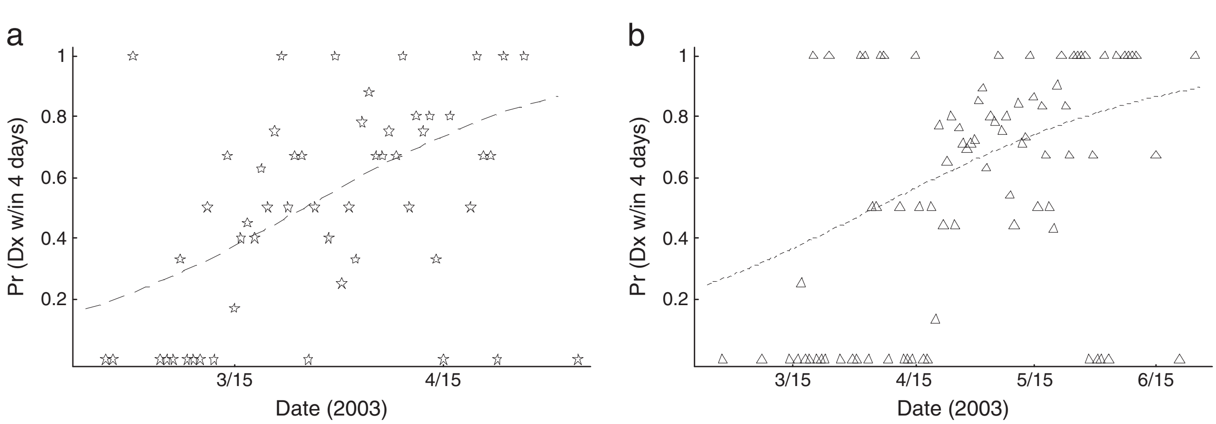

Fig. 3. a) Proportions diagnosed during the prodrome (within 4 days of symptom onset) and logistic regressions, which account for temporal variation in daily numbers of persons at risk, by onset date in Singapore and b) Taiwan. Proportions diagnosed during their prodrome increased from about 0.2 to 0.8 during both outbreaks.

contacts would suffice (as they had during the era of eradication) by observations indicating little pre-symptomatic transmission (Eichner and Dietz 2003) and substantial residual immunity among previously vaccinated members of the population (Eichner 2003). In fact, biological inaccuracies in early models (compared by Ferguson et al. 2003) caused some policymakers with firsthand knowledge of smallpox to eschew modeling.

From a policy perspective, therefore, modeling can serve many functions. Besides making qualitative predictions, models can also serve as tools or instruments with which to explore the nature of problems iteratively. Feng et al. (2009), for example, have embedded analytical results from a generic model of a respiratory disease transmitted by close contact, but about which little else is known, in software that permits end users to explore a variety of possible responses. With such a modeling environment, one can evaluate control efforts for SARS, deduce the more general results of Day et al. (2006) and Fraser et al. (2004), and possibly even guide official responses during future emergences of new human diseases. Models should not serve as the sole basis for policy decisions, but they are at least capable of illustrating the consequences of alternatives, including inaction, in a manner readily appreciable by policy makers.

While it certainly is easier to publish modeling studies in periodicals catering to mathematicians, the people whose decisions modelers hope to inform are more likely to read medical or general science journals. A dominant theme in the modeling literature about vaccine-preventable diseases, for example, is that everyone need not be vaccinated to control transmission. Indeed, to protect those who cannot receive live vaccines or who respond poorly, if at all (e.g., elderly people), it is essential to vaccinate those who might otherwise infect them. Thus, while endeavoring to “stockpile enough [smallpox] vaccine for every man, woman, and child” (Thompson 2002) may have reassured an electorate whose homeland had recently been violated, it also may have generated an expectation that will haunt us in future (when, e.g., production problems lead to shortages of influenza vaccine). Clearly, in this era of evidence-based medicine, a bridge between the two worlds must be forged to get all relevant information (even if model-based) to those charged with applying it through the expenditure of taxpayer dollars.

Summary

Public health officials must decide how to deploy available resources most advantageously. Modelers can contribute to their decision making by exploring the impact of alternative scenarios. Lest results be misleading, however, models must be faithful to available information, including expert opinion. Knowledgeable public health practitioners might have cautioned against overestimating the potential impact of managing contacts of SARS patients, and interpreted observations suggesting that infected people were not particularly infectious until acutely ill as an indication for managing cases instead. In retrospect, we might encourage policymakers to interpret the progressive shortening of intervals between symptom onset and isolation characterizing most if not all SARS outbreaks as tangible evidence of the potential of effective health communications, which could be invaluable in future crises. Absent such observations, conveying complex and occasionally nonintuitive results supporting policy decisions to public health and medical professionals is challenging. Lay audiences are even more difficult. By virtue of age variation in vaccine efficacy, for example, modelers know that people at risk of influenza complications may be better protected by vaccinating those who might otherwise infect them than by being vaccinated themselves (Bansal et al. 2006). But do health policymakers? Nonetheless, where infectious diseases are concerned, citizens likely will act in ways they perceive as congruent with their own survival or self-interest, and that of their loved ones. Effective risk communication, including balanced presentations of modeled outcomes, ensures that the self-interested actions of individuals align with socially desirable outcomes.

Disclaimers

The opinions expressed by authors do not necessarily reflect those of the Centers for Disease Control and Prevention or other institutions with which they are affiliated.

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References

Anderson, R.M., Fraser, C., Ghani, A.C., Donnelly, C.A., Riley, S., Ferguson, N.M., Leung, G.M., Lam, T.H., Hedley, A.J., 2004. Epidemiology, transmission dynamics and control of SARS: the 2002–2003 epidemic. Phil. Trans. R. Soc. Lond. B. 359, 1092–1105.

Bansal, S., Pourbohloul, B., Meyers, L.A., 2006. Comparative analysis of influenza vaccination programs. PLoS Med. 3, 1816–1825.

Chen, M.I., Leo, Y.S., Ang, B.S., Heng, B.H., Choo, P., 2006. The outbreak of SARS at Tan Tock Seng Hospital—relating epidemiology to control. Ann. Acad. Med. Singapore 35, 317–325.

Cheng, P.K., Wong, D.A., Tong, L.K., Ip, S.M., Lo, A.C., Lau, C.S., 2004. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. Lancet 363, 1699–1700.

Day, T., Park, A., Madras, N., Gumel, A., Wu, J., 2006. When is quarantine a useful control strategy for emerging infectious diseases? Am. J. Epidemiol. 163, 479–485.

Donnelly, C.A., Ghani, A.C., Leung, G.M., Hedley, A.J., Fraser, C., Riley, S., Abu-Raddad, L.J., Ho, L.M., Thach, T.Q., Chau, P., Chan, K.P., Lam, T.H., Tse, L.Y., Tsang, T., Liu, S.H., Kong, J.H.B., Lau, E.M.C., Ferguson, N.M., Anderson, R.M., 2003. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 361, 1761–1766.

Eichner, M., 2003. Analysis of historical data suggests long-lasting protective effects of smallpox vaccination. Am. J. Epidemiol. 158, 717–723.

Eichner, M., Dietz, K., 2003. Transmission potential of smallpox: estimates based on detailed data from an outbreak. Am. J. Epidemiol. 158, 110–117.

Feng, Z., Yang, Y., Xu, D., Zhang, P., McCauley, M.M., Glasser, J.W., 2009. Timely identification of control strategies for emerging infectious diseases. J. Theor. Biol. 259, 165–171.

Ferguson, N.M., Keeling, M.J., Edmunds, W.J., Gani, R., Grenfell, B.T., Anderson, R.M., 2003. Planning for smallpox outbreaks. Nature 425, 681–685.

Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S., 2006. Strategies for mitigating an influenza pandemic. Nature 442, 448–452.

Fraser, C., Riley, S., Anderson, R.M., Ferguson, N.M., 2004. Factors that make infectious disease outbreaks controllable. Proc. Natl Acad. Sci. USA 101, 6146–6151.

Germann, T.C., Kadau, K., Longini, I.M., Macken, C.A., 2006. Mitigation strategies for pandemic influenza in the United States. Proc. Natl Acad. Sci. USA 103, 5935–5940.

Goh, K.T., Cutter, J., Heng, B.H., Ma, S., Koh, B.K.W., Kwok, C., Toh, C.M., Chew, S.K., 2006. Epidemiology and control of SARS in Singapore. Ann. Acad. Med. Singapore 35, 301–316.

Hatchett, R.J., Mecher, C.E., Lipsitch, M., 2007. Public health interventions and epidemic intensity during the 1918 influenza pandemic. Proc. Natl Acad. Sci. USA 104, 7582–7587.

He, Z., Zhuang, H., Zhao, C., Dong, Q., Peng, G., Dwyer, D.E., 2007. Using patient-collected clinical samples and sera to detect and quantify the severe acute respiratory syndrome coronavirus (SARS-CoV). Virol. J. 4, 32. doi:10.1186/1743-422X-4-32.

Heesterbeek, J.A.P., 2002. A brief history of $\mathfrak{R}_0$ and a recipe for its calculation. Acta Biotheor. 50, 189–204.

Hong Kong DOH 2003. Outbreak of severe acute respiratory syndrome (SARS) at Amoy Gardens, Kowloon Bay, Hong Kong: main findings of the investigation. 17 April 2003.

Hsieh, Y.H., King, C.C., Chen, C.W., Ho, M.S., Lee, J.Y., Liu, F.C., 2005. Quarantine for SARS, Taiwan. Emerg. Infect. Dis. 11, 278–282.

Kaplan, E.H., Craft, D.L., Wein, L.M., 2002. Emergency response to a smallpox attack: the case for mass vaccination. Proc. Natl Acad. Sci. USA 99, 10935–10940.

Leung, G.M., Hedley, A.J., Lam, T.H., Ghani, A.C., Donnelly, C.A., Fraser, C., Riley, S., Ferguson, N.M., Anderson, R.M., 2005. Transmission dynamics and control of the viral aetiological agent of SARS. Blackwell Publishing, Oxford, pp. 111–130.

Lipsitch, M., Cohen, T., Cooper, B., Robins, J.M., Ma, S., James, L., Gopalakrishna, G., Chew, S.K., Tan, C.C., Samore, M.H., Fisman, D., Murray, M., 2003. Transmission dynamics and control of severe acute respiratory syndrome. Science 300, 1966–1970.

Lloyd-Smith, J.O., Galvani, A.P., Getz, W.M., 2003. Curtailing transmission of severe acute respiratory syndrome within a community and its hospital. Proc. R. Soc. Lond. B 270, 1979–1989.

Menon, K.U., 2006. SARS revisited: managing outbreaks with communications. Ann. Acad. Med. Singapore 35, 361–367.

Ou, J., Li, Q., Zeng, G., Dun, Z., Qin, A., Fontaine, R.E., 2003. Efficiency of quarantine during an epidemic of severe acute respiratory syndrome—Beijing, China, 2003. MMWR Morb. Mortal. Wkly. Rep. 52, 1037–1040.

Pang, X., Zhu, Z., Xu, F., Guo, J., Gong, X., Liu, D., 2003. Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing, 2003. JAMA 290, 3215–3221.

Peiris, J.S., Chu, C.M., Cheng, V.C., Chan, K.S., Hung, I.F., Poon, L.L., 2003. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361, 1767–1772.

Riley, S., Fraser, C., Donnelly, C.A., Ghani, A.C., Abu-Raddad, L.J., Hedley, A.J., Leung, G.M., Ho, L.M., Lam, T.H., Thach, T.Q., Chau, P., Chan, K.P., Lo, S.V., Leung, P.Y., Tsang, T., Ho, W., Lee, K.H., Lau, E.M.C., Ferguson, N.M., Anderson, R.M., 2003. Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. Science 300, 1961–1965.

Tan, C.C., 2005. Public health response: a view from Singapore. In: Peiris, M., Anderson, L., Osterhaus, A., Stohr, K., Yuen, K.-Y. (Eds.), Severe acute respiratory syndrome: a clinical guide. Blackwell Publishing, Oxford, pp. 139–164.

Tan, C.C., 2006. SARS in Singapore—key lessons from an epidemic. Ann. Acad. Med. Singapore 35, 345–349.

Thompson, T.G., 2002. Adventis Smallpox Event. Washington, DC. March 29, 2002.

Wallinga, J., Teunis, P., 2004. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am. J. Epidemiol. 160, 509–516.

World Health Organization, 2003. Consensus document on the epidemiology of severe acute respiratory syndrome. http://www.who.int/csr/sars/en/WHOconsensus.pdf.