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Epidemiological and genetic analysis of severe acute respiratory syndrome

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The severe acute respiratory syndrome (SARS) epidemics in 2002–2003 showed how quickly a novel infectious disease can spread both within communities and internationally. We have reviewed the epidemiological and genetic analyses that have been published both during and since these epidemics, and show how quickly data were collected and analyses undertaken. Key factors that determine the speed and scale of transmission of an infectious disease were estimated using statistical and mathematical modelling approaches, and phylogenetic analyses provided insights into the origin and evolution of the SARS-associated coronavirus. The SARS literature continues to grow, and it is hoped that international collaboration in the analysis of epidemiological and contact-network databases will provide further insights into the spread of this newly emergent infectious disease.

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The rapid worldwide spread of the coronavirus (figure) that causes severe acute respiratory syndrome (SARS) led to 29 countries reporting cases in 2003. The first human case was identified in Guangdong Province, China on Nov 16, 2002, and the last known case of the initial epidemic experienced the onset of symptoms on June 15, 2003, in Taiwan. (However, due to differences in case definitions, the USA has reported probable cases of SARS with onset of illness after July 5, 2003) Subsequent cases have arisen in Singapore, Taiwan, and China (most recently in April, 2004) because of laboratory-related infections and onward transmission. Worldwide surveillance, coordinated by WHO, resulted in the identification of 8098 clinically affected SARS cases, of whom 774 died.

SARS is believed to be zoonotic in origin, with the palm civet cat (Paguma larvata) being implicated as an important animal reservoir, although evidence of infection has been identified in other species (the raccoon dog, Nyctereutes procyonoides, and the Chinese ferret-badger, Melogale moschata). Close human–animal contact was associated with many early SARS cases, indicating that the SARS coronavirus had jumped host, although most of the infections over the course of the epidemic were due to human–human transmission. The spread of infectious diseases, such as SARS, within human hosts is facilitated by our increasingly mixed and densely packed global society with its high degree of connectedness through increased long-distance air travel, continued growth in world population, and increasing number of densely...
inhabited urban areas, which are particularly common in Asia.\textsuperscript{22}

Although the emergence of SARS was recent, a wide range of epidemiological studies have been published both during and since the 2003 epidemics. Increasingly sophisticated techniques and more powerful computers now permit rigorous epidemiological and genetic analysis of epidemics as they unfold. The goals of such analyses include the following: understanding the origin of the disease with a view to preventing subsequent outbreaks; estimation of key biological and epidemiological parameters; identification of risk factors for susceptibility, infectiousness, and mortality; prediction of future trends in infection and case incidence; and assessment of the effectiveness of public-health control measures. Some of these goals can be achieved through the application of widely-used epidemiological methods, such as case-control studies,\textsuperscript{23} which are applicable to a wide range of medical conditions. However, others require techniques specifically designed for the analysis of infectious diseases,\textsuperscript{24} which, although less widely used, have a long history.\textsuperscript{15–19}

Here we review the epidemiological literature on SARS, as an example of an important novel infectious disease, and consider the contributions of the various approaches. In doing so, we highlight the benefits that were realised from epidemiological analyses and to suggest how, in future outbreaks, such methods might be used even more effectively.

**Evolution of the SARS coronavirus genome**

Unprecedented levels of international cooperation led to the sequencing of two SARS viral genomes within 6 weeks of the identification of atypical pneumonia in Hong Kong.\textsuperscript{20,21} Alignment to the genomes of known groups 1, 2, and 3 coronaviruses showed that SARS coronavirus is phylogenetically distinct, and only distantly related to the other coronavirus clades. These early analyses showed that SARS coronavirus is not a recently evolved pathogen, and group 4 was proposed within which to classify the novel coronavirus.\textsuperscript{22,23} Subsequent alignment of the SARS coronavirus replicase open reading frame (ORF) 1b (about 5500 bp) genome segment, using the genus Torovirus (order Nidovirales) to root the tree, suggested that SARS coronavirus represents an early split-off from the coronavirus group 2 lineage\textsuperscript{24} and should be thought of as a group 2 subgroup. This result has found support from other studies using alternative outgroups\textsuperscript{23,24} and methods.\textsuperscript{25–27}

However, as clearly shown by analyses of other coronaviruses,\textsuperscript{23,25} single-stranded RNA viruses are prone to recombination within and between lineages. This greatly complicates phylogenetic analyses, as different regions of the genome will have different evolutionary histories. Marr and colleagues\textsuperscript{26} proposed that SARS coronavirus may have undergone intergroup recombination after noting that the SARS coronavirus S2m motif is found in the group 3 avian coronaviruses, as well as the more distantly related equine rhinovirus (Picornaviridae). Later studies focused on the SARS coronavirus spike (S), matrix (M), nucleocapsid (N), replicate polyprotein (PP1ab), and RNA-dependent RNA polymerase (RDRP) proteins with Bayesian techniques.

Here, phylogenetic incongruence was reported to occur across the SARS coronavirus genome, by showing that the M and N genes were most likely to have originated from an ancestral bird (group 3) coronavirus, whereas PP1ab showed homology with a mammalian-like (group 2) coronavirus.\textsuperscript{24} Sliding-window approaches suggested that the S and RDRP genes are candidate mosaic sequences and identified the possible site of the original interlineage recombination events.\textsuperscript{23–25} It has been proposed that recombination in the crucial S protein may have generated a virus with modified host specificities, leading to the contemporary emergence in human populations.\textsuperscript{26} An event of similar nature may have led to the 1918 Spanish influenza pandemic. However, the bootstrap methods used\textsuperscript{23,24} support an independent, and genetically distant, SARS coronavirus clade for all genes. This suggests that any recombination events, if they have occurred, are evidently ancient and therefore not implicated in the current emergence of SARS coronavirus in human populations.

**Origins and dating the emergence of human SARS coronavirus**

Retrospective assessments of case reports identified 11 index cases from the Guangdong Province, China, the earliest of which was recorded from the city of Foshan on Nov 16, 2002.\textsuperscript{10} These index cases were unlinked, except for the epidemiological observation that seven of the 11 patients worked with animals in the food industry.\textsuperscript{31} Within live-animal markets in Guangdong Province, 13–40% of wild-animal traders and slaughterers were seropositive for SARS;\textsuperscript{32} these findings led to the speculation that SARS is a zoonosis from an unidentified animal source. Suspicion focused on palm civet cats because 73% of the traders primarily trading in masked palm civet cats tested seropositive for the virus.\textsuperscript{23}

PCR and serological surveys of 25 animals from the live-animal market found serological evidence for infection in five Himalayan palm civet cats, a raccoon dog, and a Chinese ferret-badger. Coronavirus were successfully isolated from the palm civet cats and raccoon dog, yielding two full-length genomes with 99·8% homology to human SARS coronavirus.\textsuperscript{24} Further surveys of civet cats farmed in Hubei Province have shown that these too are infected with a SARS-like coronavirus.\textsuperscript{33} Comparative analyses of the Shenzhen civet cat sequences against those from 11 human isolates showed that the human and animal isolates are phylogenetically distinct.\textsuperscript{34} The genetic distance between civet cat coronavirus isolates is greater than that observed between geographically (China, Hong Kong, Canada) and temporally separated (early and mid-epidemic) human SARS coronavirus isolates.\textsuperscript{35} These data suggest that SARS originated from an animal reservoir, and that the ultimate source of the coronavirus that caused the emergence of the human SARS coronavirus genotype remains unclear. However, sequence data from a recent case (GD05T0013, isolated Dec 16, 2003) has found closer grouping with the civet cat coronaviruses than was previously observed,\textsuperscript{31} suggesting that civet cats may indeed be the source of SARS coronavirus. Further attempts to isolate the virus from...
market animals has met with little success. \(^{34-36}\) Final confirmation of the animal reservoir of SARS coronavirus therefore awaits a systematic survey of Chinese fauna.

By May 9, 2003, 14 genomes of SARS coronavirus had been sequenced. \(^{7}\) This total has risen to 100 GenBank depositions by May, 2004. Molecular analyses have shown that the early phase of the epidemic was characterised by two genotypes. The first (cluster A) is composed of 10 isolates corresponding to the very early cases from Guangdong Province and three separate introductions to Hong Kong. \(^{30}\) The second (cluster B) corresponds to the so-called super-spreading event (SSE) triggered by the arrival of patient 1 (HKU-33) in Hong Kong. \(^{33,35}\) This is the genotype that ultimately became pan-global. The finding that most of the SARS coronavirus genetic diversity occurs within cluster A is consistent with the epidemiological observations that Guangdong Province, China, is the geographical point of origin for the emergence of the virus.

If we assume that SARS coronavirus had a single emergence within human populations, the most recent common ancestor of SARS coronavirus will correspond to our best approximation for the emergence of the virus. Efforts to date the most recent common ancestor of SARS coronavirus have mostly followed the rationale that was used to date the emergence of HIV-1 M group viruses. \(^{36}\) This relies on building a phylogenetic tree of isolates to find the most deeply branched sequences, then assuming neutral clock-like evolution to date the root of the tree. Using the divergence of S-gene sequences from 139 patients, \(^{37}\) linear regression dated the emergence of SARS coronavirus to mid-December, 2002 (95\% CI late September, 2002, to mid-January, 2003). \(^{38}\) A recent study by the Chinese SARS Molecular Epidemiology Consortium \(^{31}\) attempted to correct for the potential effects of selection by only using synonymous (\(K_s\)) substitutions. They dated the ancestral sequence with the deeply rooted isolate GZ02 as an outgroup, and estimated an origin of mid-November, 2002 (95\% CI early June, 2002, to late December, 2002). If correct, these data suggest that the earliest known SARS case, in November, 2002, was not far removed from the theoretical origin of the epidemic.

However, although promising, these studies necessarily rely on isolates that are collected over a short timescale and are probably rapidly evolving. Whereas contemporary isolates are rare, there have been recent infections that are not associated with laboratory escapes. \(^{39}\) Due to the observation that the isolate GD03T0013 is the most deeply rooted yet seen, use of this sequence to date the most recent common ancestor of SARS coronavirus will push back the epidemic’s origin, perhaps significantly. If done, such an analysis would suggest that SARS coronavirus has been circulating, undetected, in China for longer than was previously expected. It is also evident from comparisons of non-synonymous to synonymous substitution rates (\(K_a/K_s\)) in the S protein that the SARS genome is under strong directional selection. \(^{40}\) The use of techniques that account for variation in the rates of evolution over the course of the epidemic (ie, Bayesian evolutionary analysis sampling trees, BEAST v1.0.2, available from http://evolve.zoo.ox.ac.uk/ beast/ [accessed Oct 4, 2004]) would therefore be appropriate.

**Incubation period**

A key factor in the epidemiology of an infectious disease is the incubation period, which is defined as the time from infection to onset of clinical symptoms of disease. \(^{41}\) The distribution of the incubation period has important implications for contact tracing and quarantine strategies, so accurate estimates of the distribution are an important goal for early epidemiological investigations of a novel disease. Furthermore, the average incubation period influences the timescale of the development of the epidemic, as it partly determines the time interval between a case and the infections that the case subsequently generates. Identification of determinants of the incubation period, such as age, infectious dose, and host genetics, can provide insights into the mechanisms of disease progression.

Although infection events cannot be observed directly, some patients retrospectively reported well-defined periods of exposure to one or more known SARS cases. When an event (ie, infection) is only known to have occurred within a defined period, the data are said to be interval censored. \(^{42}\) Patients with long periods of exposure are uninformative; however, patients with short and well-defined periods of exposure are informative, even though the exact date of infection is unknown. These data, when analysed appropriately, can be used to estimate the distribution of incubation periods in the patient population.

Summaries and analyses of incubation period data have been published for various populations of patients (table 1). In many cases, the difficulties posed by interval censoring led to researchers presenting descriptive summary statistics without further analysis. Other work corrected for the interval censoring by use of both parametric \(^{43}\) and non-parametric \(^{44}\) approaches. However, it should be noted that naive analyses that assume patients were equally likely to have been infected throughout their reported interval \(^{45}\) overestimate the variance in the distribution and could also bias the estimates of the mean incubation period, with the size of these problems depending on the width of the reported exposure intervals.

Given the difficulties inherent in the interpretation of interval-censored data, the central estimates (means and medians; table 1) are remarkably consistent in patients in China, Hong Kong, Singapore, and Canada (with central estimates ranging from 4 to 6). The mean from European cases, 7·2 days, was somewhat higher, but the estimate is uncertain because it is based on only five cases. \(^{46}\)

The maximum incubation period is less clear, with a number of reports of incubation periods exceeding WHO’s maximum incubation period of 10 days. \(^{47,48}\) The WHO consensus document on the epidemiology of SARS, published in October, 2003, noted the existence of incubation period outliers of more than 10 days, but suggested they had “not necessarily been subjected to rigorous and standardised investigation”. \(^{49}\) Furthermore, interval censoring causes particular difficulties in assessing the maximum incubation period, and if midpoints in large
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exposure intervals are relied on then errors can result. For example, an incubation period in a patient exposed to a SARS case 5–25 days before symptom onset might be naively (and most likely incorrectly) reported as a 15-day incubation period.

Three studies reported somewhat higher mean incubation periods (8, 7·3, and 7·6 days). Similarly, another group reported that, although the index case had an incubation period of 4 days, the secondary and tertiary generations had incubation periods of 7 and 8 days, respectively, noting that shorter incubation periods were associated with longer fevers and greater clinical severity. By contrast, He and colleagues reported a mean incubation period of 4–5 days in patients from Guangdong Province, China, and Li and colleagues reported a median incubation period of 3 days (range 1–10 days) in Beijing, China. However, we were unable to obtain full translations of these papers so were not able to determine how these estimates were obtained.

Since only a small proportion of the SARS cases will have data suitable for estimation of the incubation period distribution, international collaboration would be particularly valuable. (WHO has suggested that such data exist on only 200 cases worldwide.) Such efforts would, however, need to go well beyond straightforward analysis of a merged dataset, due to the care and precision required to define periods of exposure to SARS infection accurately. If an international dataset were systematically compiled, then rigorous overall estimates of the incubation period distribution could be obtained, and any dependence of the

Table 1. Published data on the incubation period of SARS

| First author | Publication date | Location | Number of patients | Interval censoring (IC) or multiple exposure | Other comments | Estimates (days) |
|--------------|-----------------|----------|--------------------|---------------------------------------------|---------------|-----------------|
| Tsang^a      | March 31, 2003  | Hong Kong| 9                  | IC present in 5 of 9,..                      | Individual data published | Range 2–7       |
| WHO^a        | March 21, 2003  | Worldwide| ..                 | IC present                                  | Individual data published | Median 6, range 2–16 |
| Poutanen^a   | March 31, 2003  | Canada  | 10                 | Unclear, described as "the interval between exposure to the index patient or ward and the onset of fever" | Range and median reported | Median 6, IQR 3–10 |
| Lee^b        | April 7, 2003   | Hong Kong| ..                 | Some multiple exposures                     | Reported median and IQR from earliest self-reported exposure to onset of symptoms (caution urged) | Mean 3–8, variance 8–3 |
| Booth^b      | May 6, 2003     | Canada  | 144                | ..                                           | Maximum likelihood allowing for IC | Maximum 10        |
| Donnelly^b   | May 7, 2003     | Hong Kong| 57                 | IC present, estimates based on patients with single exposure | Mean, median, 95th percentile reported; gave separate estimates for those with "well-defined point exposures"; mid-points used for IC data. | Mean 5, median 5 |
| WHO^a        | May 7, 2003     | Worldwide| ..                 | IC present                                  | Mean, median, range reported | Mean 5, median 4-3 |
| Leo^b         | May 9, 2003     | Singapore| 21 patients with point exposures; 94 with *well-defined exposures* | Mean and range reported | Mean 5-9, range 1–20 |
| Wu^b         | June, 2003      | Guangzhou, China| ..                 | Mean and range reported | Mean 4, SD 3 (single exposure); mean 3-5, SD 3 (multiple exposure) |
| Avendano^c    | June 24, 2003   | Canada  | 14*                | 4 with single exposure and 10 with multiple exposure | Mean and SD reported separately for patients with single and multiple exposures | Mean 4, median 5, range 2–10 |
| Varia^c       | July 29, 2003   | Canada  | 42                 | ..                                           | Mean and range reported | Median 5          |
| Choi^c       | Oct 1, 2003     | Canada  | 10                 | ..                                           | Mean and range reported | Median 5          |
| WHO^c        | Oct 17, 2003    | Singapore, Guangdong, China; WHO European Region | 46 | Single exposure, IC not mentioned | Mean, median, range reported | Mean 4, median 5, range 1–10 |
| Olsen^d      | Dec 18, 2003    | In-flight transmission | 22 | IC and multiple exposure not present due to limited (in-flight) exposure | Mean and range reported, full data given in figure | Mean 4, range 2-8 |
| Chow^e       | Jan 15, 2004    | Singapore| 15                 | Multiple exposures present; "complex" Present; all data published | Range reported and full data given in figure | Mean 4-3, median 4, variance 2-2, range 3–8 |
| Metzger^e    | Feb, 2004       | Hong Kong, Canada, USA | 20† |   | Assumed uniform distribution to allow for IC to estimate distribution | Median 4, range 1–18 |

*These 14 patients were among the 144 SARS patients previously described by Poutanen and colleagues; however, this study only reported incubation period information for patients with single exposures, whereas Avendano and colleagues reports data for both singly and multiply exposed patients. †The data analysed include those published by Tsang and colleagues and Poutanen and colleagues in addition to previously unpublished data on two USA patients. ..=not specified.
incubation period distribution on patients’ characteristics (ie, age, sex, stage of the epidemic) could be determined.

**Infectiousness and disease progression**

Following the appearance of symptoms, virtually all SARS patients were either admitted to hospital or placed under home quarantine. Disease progression was best summarised by Peiris and colleagues\(^4\) who followed 75 SARS patients for 3 weeks after admission to hospital in Hong Kong. Patients experienced a recurrence of symptoms after a mean of 8·9 days, a peak in viral load at approximately 10 days after admission, and 60% of patients had seroconverted by 20 days. The rates of admission to intensive care units (ICUs) in cohorts worldwide ranged from 23% to 40%, with a high proportion of those admitted with acute respiratory distress syndrome and requiring mechanical ventilation.\(^6\)\(^-\)\(^9\)

Transmission of SARS in most cases could be linked to direct close contact with another SARS case. Many of these contacts were nosocomial. Roughly half of cases were healthcare workers, in studies in Hong Kong\(^6\) and Guangzhou, China,\(^2\) and 77% of cases were exposed in hospital, in a study from the Toronto area, Canada.\(^6\)

Although these studies are convenience samples drawn from particular hospitals, the levels reported are similar to those reported from the national database of SARS cases in Hong Kong (with 49% of the SARS cases resulting from infections occurring in clinics, hospitals, or elderly or nursing homes; G M Leung, Department of Community Medicine, University of Hong Kong, personal communication).

Within the community, rates of transmission were generally low, with 8% of household contacts infected in one study in Hong Kong\(^3\) and 6·7% in a study in Singapore.\(^3\) The closeness of contact also seems to be important. For example, in a large retrospective examination of case notes of quarantined close contacts of SARS cases in Beijing, China, the overall attack rate was 6·3%, with the highest rates (15·4%) in spouses and lowest rates in work and school contacts (0·36%).\(^7\) These figures are further supported by large-scale screening for SARS coronavirus antibodies in direct contacts of SARS cases, which have very low rates (0·2%) were positive for SARS coronavirus IgG antibodies.\(^3\)

Nosocomial transmission therefore seems to have been the major source of new infections, with higher attack rates reported in this setting. For example, in a study of nosocomial outbreak in Toronto, rates in nurses working in the emergency department, ICU, and coronary care unit ranged from 10% to 60%.\(^3\)

Good barrier protection was essential to prevent transmission: in a case-control study in Hong Kong, inconsistent use of goggles, gowns, gloves, and caps was significantly associated with a higher risk of SARS.\(^3\)

**Case fatality rate**

Early in the epidemic, with little known about the pathogenicity of SARS, there was substantial concern about the increasing rates of morbidity and mortality that were being reported through individual case reports. Estimation of the case fatality rate (CFR; the percentage of people diagnosed as having a specific disease who die as a result of that disease) during an outbreak is complicated because the eventual outcomes of patients still in hospital are unknown at the time of analysis. The duration of hospital stay depended on the severity of illness, but for most patients this was in the region of 14 days to 1 month.\(^6\)\(^-\)\(^7\) Naive estimates of the CFR, based simply on the cumulative number of deaths divided by the cumulative number of cases,\(^7\) were therefore particularly misleading because they yielded underestimates of the true mortality. This bias was reduced as the epidemic progressed (and as the outcome of a greater percentage of patients was known), which is why reported estimates of CFR seemed to indicate that mortality was increasing over time, causing some to incorrectly conclude that SARS coronavirus was evolving to be more lethal.\(^2\)\(^-\)\(^7\) The earliest estimates that used appropriate statistical methodology were published in May, 2003, with data from Hong Kong\(^2\) and worldwide,\(^2\) and gave final CFR estimates of between 14% and 18%. Table 2 shows the estimates obtained in various cohorts, with CFRs at 21 days after hospital admission of 6·5% and 10%, at 28 days of 10%, and at 3 months of 12%.\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) CFRs for those admitted to ICUs were significantly higher, with estimates at 28 days of 26% and 34% in Hong Kong and Toronto cohorts, respectively.\(^6\)\(^-\)\(^7\)

Several cohorts have consistently described the course of disease for SARS patients, using these data to assess factors that contribute to an increased risk of an adverse outcome. The definition of adverse outcome varies, but generally includes death, admission to an ICU requiring mechanical ventilation, and development of acute respiratory distress syndrome. Most studies identify older age as a factor that increases the probability of an adverse event.\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) The strong association between age and CFR is also clearly seen in national case reports, with CFR estimates in those aged over 60 years particularly high.\(^6\)

The presence of co-morbidities, including diabetes mellitus, hypertension, coronary artery disease, and chronic obstructive pulmonary disease, also significantly increased the risk of adverse outcomes and death from SARS\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) and probably helps to explain the strong association between the CFR and age. Indeed, in some cohorts, deaths almost exclusively occurred in patients with other co-morbidities.\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) Other notable factors contributing to higher CFRs were sex (with men at higher risk than women),\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) high lactate dehydrogenase concentration at presentation,\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) and higher viral loads.\(^6\)

Most patients with SARS received some treatment that was based on previous experience with respiratory infections and evolved over the course of the epidemic. For this reason, most reports of the success of different treatments are observational and may be subject to treatment allocation bias. Common treatments included administration of antibiotics, ribavirin, and corticosteroids,\(^6\)\(^-\)\(^7\)\(^9\)\(^-\)\(^10\) with the HIV-1 antiviral drug lopinavir also tested later in the epidemic in Hong Kong.\(^6\)

In one study in Guangzhou, China, patients were randomly allocated to one of four treatment regimens, with the best response seen in the group receiving early high-dose steroids.\(^6\)

However, as was the case...
for the observational studies, the study was not fully randomised since this fourth group consisted of patients diagnosed later in calendar time than the other three groups.

Transmission dynamics of SARS

Traditional epidemiological approaches cannot be used to assess the population-level risk posed by an emerging infectious disease. The expected number of cases on any given day is determined by the current size of the outbreak, the transmissibility of the disease, and the mixing behaviour of the population, with the infection process causing positive feedback, which results in highly non-linear trends in case incidence over time. Mathematical epidemic models describe (with varying levels of realism) the underlying mechanisms and dynamics of disease progression in the infected individual and transmission in the population. They are therefore also known as mechanistic or dynamical models. It is now common practice for the continuing population-level risk from infectious disease to be assessed using such models.

The most important concept underlying the dynamics of infectious disease epidemics is that of the reproduction number $R_t$. This is defined to be the average number of new infections caused by one infectious case, over the whole course of that individual’s infectious period. At the very start of an outbreak ($t=0$), the basic reproduction number, $R_0$, is defined to be the average number of secondary cases caused by the index case in an entirely susceptible population. If $R_0$ is greater than 1, then an infectious disease outbreak has the potential to establish itself, resulting in an epidemic that will infect a substantial proportion of the population if there is no significant change in either the behaviour (ie, reduced

| First author | Publication date | Location | Number of patients | Analysis method | Estimated mortality rate | Significant correlates | Non-significant factors |
|--------------|------------------|----------|--------------------|----------------|-------------------------|-----------------------|------------------------|
| Lee**        | April 7, 2003    | Hong Kong | 138                | Logistic regression | 3-6% died by day 21 | Age (p=0.007)          | Sex (p=0.01)            |
| WHO**        | April 11, 2003   | Worldwide | 2781               | Deaths divided by SARS cases | 4% | Age: higher death rate in older patients in Canada |
| Booth**      | May 6, 2003      | Canada   | 144                | Proportional hazards multivariate analysis | 6-5% at 21 days | Diabetes: RR 3-1 (95% CI 1.4–7.2) | Other comorbid disease:* RR 2.5 (95% CI 1.1–5.8) |
| Donnelly**   | May 7, 2003      | Hong Kong | 1425               | Non-parametric and parametric estimation allowing for censoring | 14-9% (non-parametric) 18.2% (parametric) | Age (non-parametric): <60 years 6-8%, >60 years 55.0% Age (parametric): <60 years 13.2%, >60 years 43.3% |
| WHO**        | May 7, 2003      | Worldwide | --                 | “More reliable methods” than used previously* | 14–15% overall: 11–17% Hong Kong, 13–15% Singapore, 15–19% Canada, 5–13% China | Age: <25 years <1%, 25–44 years 6%, 45–64 years 15%, >65 years >50% |
| Fowler**     | July 16, 2003    | Toronto  | 38 adults admitted to ICU | Fisher’s exact test and logistic regression | 34% at 28 days | Age, diabetes |
| Lew**        | July 16, 2003    | Singapore | 199                | Logistic regression of early or intermediate recovery vs late recovery or death | 10-1% at 28 days | Age: OR for 1 yr increase 1-04 (95% CI 1.01–1.09); APACHE II score: OR for 1 unit increase 12 (95% CI 1-05–1.4) | Sex, asthma, diabetes, hypertension, chronic renal failure. |
| Chan**       | Aug, 2003        | Hong Kong | 115                | Proportional hazards models | 15-7% by May 31, 2003 (outcome known in 100 patients), 10% at 21 days | Age >60 years: HR 3-6 (95% CI 2-8–29-1); other comorbid conditions:† HR 5-2 (95% CI 1-4–19-2) |
| Choi**       | Nov 4, 2003      | Hong Kong | 267                | Proportional hazards models | 12% at 3 months | Age >60 years: HR 5-1 (95% CI 2-3–11-3) |
| Shier**      | Feb, 2004        | Beijing, China | 77            | Fisher’s exact test (two-tailed) | -- | Onward transmission: 75% super-spreaders,† 16% others. |

*Defined as chronic obstructive disease, cancer, and cardiac disease. †Defined as hypertension, asthma, and chronic renal failure. 12 and colleagues arbitrarily defined super-spreaders to be those attributed as the source of SARS in at least eight other persons. HR=hazard ratio; ICU=intensive care unit; OR=odds ratio; RR=relative risk; -- not reported.
Table 3. Mathematical transmission models fitted to data

| First author | Publication date | Model* | Stochastic | Data† | Explicit SSEs | Mixing assumptions | Other key assumptions | Fitting methods | Results |
|--------------|------------------|--------|------------|-------|---------------|-------------------|----------------------|-----------------|---------|
| Razum⁹¹      | May 17, 2003     | Exponential | No         | HK 21/2-5/4 | No | Homogeneous | --                | LS to cumulative case numbers | Explains why models should not be fitted to cumulative case numbers |
| Riley⁹²      | June 20, 2003    | SEIHR/D | Yes         | HK 26/2-30/4 | Yes | Metapopulation (homogeneous within districts) | Interventions reduced both community and hospital transmission; infectiousness reduced by 80% after hospital admission; used realistic incubation distributions. | ML to incidence; used waiting times estimated from individual case reports. | $R_0$ excluding SSEs=2·7 reduced to 0·14 by end of epidemic; SSE contribution of order 0·3. |
| Lipsitch⁹³   | June 20, 2003    | SEIR   | No          | HK 15/2-28/4; World 16/11-20/5 | No | Homogeneous epidemic was assumed | The case, matched growing exponentially (i.e., there were no reductions in transmission caused by interventions). | For a given first model to final cumulative case numbers; serial interval estimated from Singapore outbreak. | $R_0 = 2.2-3.6$ |
| Branching process | Yes | | | HK 15/2-19/4 | No | Homogeneous | Assumed that there were no reductions in transmission caused by interventions. | Bayesian estimation with negative binomial distribution of secondary infections and Weibull distribution of serial intervals, both fitted to Singapore data. | $R_0$ posterior mode=2·2, 95% credible interval 1·5-7·7 |
| Galvani⁹⁴    | Aug 8, 2003      | Exponential | No         | All WHO data 15/3-11/5 | No | Homogeneous | --                | LS to cumulative case numbers. | Find a negative correlation between doubling time and CFR. $R_0 = 1.1-1.2$ |
| Chowell⁹⁵    | Sept 7, 2003     | SEIHR  | No          | World, HK, Canada, Ontario 31/3-14/4 | No | Homogeneous | Assumed the epidemic was growing exponentially. | LS to cumulative case numbers; most parameters fixed to plausible values. | $R_0 = 1·1-1·2$ |
| Ng⁹⁶         | Sept 10, 2003    | SEIR   | No          | HK 17/3-12/5; Beijing, Inner Mongolia 21/4-12/5 | No | Homogeneous | Assumed epidemic of unknown virus providing widespread protection to SARS resulted in decline in cases. | LS to cumulative case numbers. | Did not calculate $R_0$; found that the model had difficulty explaining rapid decline of case numbers. $R_0 = 1·5$, CFR=30% |
| Choi⁹⁷       | Oct 1, 2003      | SIHR/D | No          | Canada 25/2-26/5 | No | Homogeneous | Assumed discrete generations, with a fixed infectious/incubating period of 5 days and time to death or recovery of 14 days; assumed no hospital transmission. | Fitted by trial and error to cumulative case and death reports. | $R_0 = 1·1-1·3$ |
| Wang⁹⁸       | Nov 6, 2003      | SEQIR  | No          | Beijing 27/4-2/6 | No | Homogeneous | Distinguish between suspected and probable cases. | Fit empirical time-dependent rates in simplified model to incidence. | $R_0 = 2·7$ (Beijing), 2·1 (HK), 3.8 (Singapore), using method based on initial growth rate.⁹⁷ Continued on next page |
| Zhou⁹⁹       | Dec 12, 2003     | Curve fit | No         | Beijing 21/4-24/6; HK 17/3-23/6; Singapore 17/3-30/5 | No | Homogeneous | --                | LS to cumulative case numbers; fit an empirical curve. | -- |

Continued on next page
Table 3. Mathematical transmission models fitted to data (continued)

| First author | Publication date | Model* | Stochastic Data† | Explicit mixing SSEs | Other key assumptions | Fitting methods | Results |
|--------------|-----------------|--------|-----------------|---------------------|----------------------|----------------|---------|
| Waltinga     | Sept 15, 2004   | Branching process | Yes | HK, Vietnam, Singapore, Canada | No | Homogenous infectiousness | ML of who-infected-who matrix and serial interval based on Singapore data | Detailed R0 curves, reduction to 0·7 after March 12. |

*In their simplest form, such models structure individuals into three compartments: susceptible (S), infected (I), and recovered (R). With recovery assumed to be immune to further infection, for this reason, such models are often called SIR models. Extensions of SIR models have included additional classes of individuals: exposed (E), also known as latent, hospitalized (H), quarantined (Q), and dead (D).  †Region and dates from which data were obtained for analyses. CPR=case fatality rate; ML=maximum likelihood; SSE=super-spreading event; ··=not applicable.

The main benefit of mechanistic models, compared with purely descriptive models, is their ability to allow the exploration of hypothetical situations (table 4). This can take the form of examination of the impact of a range of potential control options on case incidence (such as the imposition of movement restrictions, or improved quarantine and contact tracing), or the investigation of disease spread in a novel setting (such as Japan, where there were no SARS cases). Such investigations do, by definition, involve extrapolation beyond the observed data. However, when presented with careful sensitivity analyses that show the extent to which key results depend on model assumptions, these studies can provide valuable insights to scientists and public-health policy makers.
Heterogeneity in transmission: the role of SSEs

Heterogeneity in contact rates or infectiousness has been recognised as a key factor in determining patterns of infectious disease spread for many years. However, for SARS the importance of such heterogeneity was particularly underscored by the occurrence of a few dramatic SSEs in which single individuals were responsible for infecting many times more individuals than the average (given by $R_0$). The examples of patient 1 in Hong Kong, who infected 10 people in the Metropole Hotel (known as Hotel M) and additional people after his admission to St Paul’s Hospital, Hong Kong, and the Amoy Gardens cluster in Hong Kong are the best known, but patients who generated large numbers (>10) of secondary cases were also identified in Singapore (with at least five such patients) and Canada.

However, super-spreading individuals are not unique to SARS. Their existence has been well documented for tuberculosis, measles, smallpox, and the zoonotic transmission of monkeypox. Furthermore, the importance of a small number of individuals with high rates of partner change is critical to the epidemiology of many sexually transmitted infections.

There will, of course, be variability in the number of secondary cases from any primary case owing to random variation, even without any underlying variation due to characteristics of the primary case. However, if all cases have identical levels and durations of infectiousness with constant contact probabilities, such variation is expected to be Poisson. Once variation in the duration of infectiousness period is allowed for, higher than Poisson variance is expected, with negative binomially distributed numbers of secondary cases expected for exponentially distributed infectiousness.

However, key to the debate surrounding SSEs is whether such events are merely the extreme tail of a continuous distribution or they represent a distinct separate class of cases. Although some of the SSEs (particularly those in Hong Kong) seem too extreme to have arisen from an underlying continuous distribution, it should be noted that estimating the frequency of SSEs from case data in a single region is subject to severe selection biases. This is because in

| First author | Publication date | Model* | Stochastic | Explicit SSEs | Mixing | Other key assumptions | Parameter choice | Results |
|--------------|-----------------|--------|------------|---------------|--------|----------------------|-----------------|---------|
| Riley**      | June 20, 2003   | SEIHVD | Yes        | Yes           | Meta-population (homogeneous within districts) | --               | From their best fit model (above) | Movement restrictions between districts would have been able to stop an otherwise uncontrolled Hong-Kong-like epidemic. Quarantine and accelerated isolation could be expected to control SARS. |
| Lipsitch***  | June 20, 2003   | SIEHR  | No         | No            | Homogeneous | Assumed quarantining occurred instantaneously after contact with infective; assumed patients could be perfectly isolated in hospitals. | From their best fit model (above). | |
| Lloyd-Smith**** | July 30, 2003  | SIEHR  | Yes        | No            | Separate core-group of healthcare workers, otherwise homogeneous | Assumed quarantining occurred instantaneously after contact with infective; used realistic incubation distributions. | From earlier studies. | Control of nosocomial transmission was key to controlling SARS. |
| Nishiura****  | March 1, 2004   | SIEHR  | No         | No            | Homogeneous | Same model as Lipsitch. | From Lipsitch. | If SARS were to re-emerge in an environment where it could be controlled (such as Japan), the number of people infected would most strongly depend on the initial number of cases. |
| Masuda*****   | Mar 31, 2004    | Individual-based simulation | Yes | Realistic "small-world" social network | -- | | From earlier studies and from Singapore contact tracing data. | SSEs did not arise from highly-connected individuals, but were a different transmission process; transmission patterns were not consistent with a scale-free social network. Because infectiousness does not peak until long after symptoms, SARS can be contained by isolation alone, though quarantining helps counter logistical delays; smallpox, which is more infectious, can be contained using isolation and quarantining; HIV and pandemic influenza cannot. |
| Fraser******  | April 7, 2004   | Individual-based model, with isolation and quarantining | No | Homogenous | Model explores interplay between appearance of symptoms and changing infectiousness as a function of time since infection. | Based on collated studies of SARS, HIV, influenza, and smallpox. | |

*In their simplest form, such model structures divide individuals into three compartments: susceptible (S), infected (I), and recovered (R), with recovered individuals assumed to be immune to further infection; for this reason, such models are often called SIR models. Extensions of SIR models have included additional classes of individuals: exposed (E, also known as latent), hospitalised (H), quarantined (Q), and dead (D).

| Table 4. Mathematical transmission models used to explore hypothetical situations | First publication date | Model* | Stochastic | Explicit SSEs | Mixing | Other key assumptions | Parameter choice | Results |
|-----------------------------------------------|------------------------|--------|------------|---------------|--------|----------------------|-----------------|---------|
| Riley**                                       | June 20, 2003          | SEIHVD | Yes        | Yes           | Meta-population (homogeneous within districts) | --               | From their best fit model (above) | Movement restrictions between districts would have been able to stop an otherwise uncontrolled Hong-Kong-like epidemic. Quarantine and accelerated isolation could be expected to control SARS. |
| Lipsitch***                                  | June 20, 2003          | SIEHR  | No         | No            | Homogeneous | Assumed quarantining occurred instantaneously after contact with infective; assumed patients could be perfectly isolated in hospitals. | From their best fit model (above). | |
| Lloyd-Smith****                             | July 30, 2003          | SIEHR  | Yes        | No            | Separate core-group of healthcare workers, otherwise homogeneous | Assumed quarantining occurred instantaneously after contact with infective; used realistic incubation distributions. | From earlier studies. | Control of nosocomial transmission was key to controlling SARS. |
| Nishiura****                                | March 1, 2004          | SIEHR  | No         | No            | Homogeneous | Same model as Lipsitch. | From Lipsitch. | If SARS were to re-emerge in an environment where it could be controlled (such as Japan), the number of people infected would most strongly depend on the initial number of cases. |
| Masuda*****                                 | Mar 31, 2004           | Individual-based simulation | Yes | Realistic "small-world" social network | -- | | From earlier studies and from Singapore contact tracing data. | SSEs did not arise from highly-connected individuals, but were a different transmission process; transmission patterns were not consistent with a scale-free social network. Because infectiousness does not peak until long after symptoms, SARS can be contained by isolation alone, though quarantining helps counter logistical delays; smallpox, which is more infectious, can be contained using isolation and quarantining; HIV and pandemic influenza cannot. |
| Fraser******                                | April 7, 2004          | Individual-based model, with isolation and quarantining | No | Homogenous | Model explores interplay between appearance of symptoms and changing infectiousness as a function of time since infection. | Based on collated studies of SARS, HIV, influenza, and smallpox. | |
the earliest stages of a local outbreak the occurrence of an SSE dramatically lowers the chances of that outbreak becoming extinct by chance. Therefore, SSEs are more likely to have occurred early in the outbreaks in those locations where large outbreaks were seen (eg, Toronto, Hong Kong, Singapore). Ideally, one would like to characterise the overall distribution of secondary case numbers for SARS before and after controls were introduced. To do this rigorously would require a global analysis, given the early importance of international spread. However, the detailed contact tracing data required for such an analysis does not exist in some areas, and are incomplete for others where large outbreaks were seen.

Irrespective of whether SSEs are a discrete class of transmission events or the tail of a distribution, it cannot be assumed that variation in secondary case numbers is primarily due to biological variation in the amount of virus shed by patients and hence their infectiousness. Variation in contact rates with other individuals in the population is also likely to have been important, and may indeed have been the dominant factor explaining SSEs. Such variation might be in the frequency of direct contacts (eg, large numbers of medical personnel saw the index patient in the Prince of Wales Hospital in Hong Kong19) or indirect contacts (eg, unusual modes of viral spread in the Metropole Hotel and Amoy Gardens10). Characterisation of heterogeneity in contact rates has been the topic of much research in infectious disease epidemiology, and various modelling approaches (including stratified population models and individual-based network models) have been developed to incorporate such heterogeneity. Masuda and colleagues use a network-based approach to model SARS, and concluded that SSEs are best explained by an increase in infectiousness in a few individuals, rather than extreme contact-rate heterogeneity. However, these conclusions are dependent on the investigators’ simplifying assumptions about network structure. Overall, identifying the biological, social, or environmental causes for SSEs is important for the development of strategies for efficiently preventing or controlling such events, since the optimal choice of tactics to be employed will depend on the causative mechanisms.

Conclusions

Despite the substantial achievements already made in understanding the origin and determinants of spread of the SARS epidemics, important questions remain unanswered. These include clarification of how, if at all, seasonality contributed to the epidemic patterns observed; understanding precisely how transmission took place within particular settings (eg, hospital wards); gaining insight into the extent to which differences in social networks contributed to heterogeneity in SARS transmission; and determining the zoonotic origins of the virus. Answering these questions will depend mainly on the reliability and availability of the relevant data and will require multiple methodological approaches.

For example, investigating the impact, if any, of seasonality on transmission would require coordinated modelling of the large SARS epidemics (in China, Hong Kong, Taiwan, Singapore, and Canada) to separate the effects of temporal changes in humidity, temperature, and other environmental factors from the effects of temporal changes in epidemiological factors, such as contact tracing and reduced mixing. Greater understanding of within-ward transmission would be gained into risk factors associated with both infectiousness and susceptibility from detailed stochastic modelling of patient and healthcare worker contacts. This work could usefully build on published Markov chain Monte Carlo models of nosocomial transmission.

As well as giving greater insights into processes underlying the SARS epidemic, the models and estimation methods developed will strengthen the set of analytical tools available for the analysis of future epidemics. In each case, surveillance and data quality are fundamental to providing sound foundations to underpin analyses and conclusions. Contingency plans developed on the basis of the experience of the SARS epidemics have rightly placed a high priority on both surveillance and contact tracing. More detailed modelling will be required to further clarify the potential impact of further measures, including restrictions on both short-range and long-range movements of people. A review of recent smallpox modelling cautioned that modelling efforts should not set the nearly impossible goal of identifying the best public-health strategy in advance of an epidemic, but should identify sets of recommended actions with associated decision rules for adaptive management as an epidemic unfolds.

Conflicts of interest

We declare that we have no conflicts of interest.

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