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Epidemiology of SARS in the 2003 Hong Kong epidemic

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Key Messages

1. The temporal and spatial evolution of the SARS epidemic in Hong Kong is described.
2. Estimates of key epidemiological distributions and their stability over the course of the epidemic are derived.
3. The characteristics of those who contracted the disease are determined including factors associated with the likelihood of mortality as a result of SARS-coronavirus infection.

Introduction

The SARS epidemic was the first communicable disease epidemic of the 21st century, with 29 countries affected. The first human case was identified in Guangdong, China on 16 November 2002 and the last known case had a symptom onset date of 5 July 2003 in Taiwan. The disease infected 8098 individuals of whom 774 died.[1,2] Hong Kong bore a large proportion of this morbidity and mortality burden, and was the link between cases in China and other parts of the world. Of 1755 cases, 299 deaths occurred from 15 February to 31 May 2003.

To formulate public health policy, an account of the epidemiology of SARS in Hong Kong was undertaken during the outbreak.[3] The dataset has since been updated using information from all 1755 reported cases. Relaxation of parametric assumptions was allowed in the mid-epidemic analysis, in the analysis of the interval from symptoms to admission, admission to death, and admission to discharge. Furthermore, complete case data enabled analysis of predictors of SARS-related mortality using logistic regression.

Aims and objectives

To generate and delineate the definitive epidemiological parameters of SARS-CoV, using the complete case-contact data from the 2003 Hong Kong outbreak.

Methods

Sources of data

We analysed an integrated database (SARSID) derived from the Hong Kong Hospital Authority eSARS system (a secure web-based data repository containing mostly real-time clinical data). Some data fields were collected/confirmed retrospectively via a detailed chart review (according to a standardised protocol by trained nurses) and the Department of Health's Master List (consisting mostly of questionnaires of case and case-contact data). The latter contained details on all SARS patients admitted to hospitals in Hong Kong throughout the entire epidemic. The questionnaires (exploring case and case-contact information) were administered, mostly through telephone interviews, with all SARS patients (in whom the diagnosis were confirmed by the Department of Health). The interviews were conducted mostly within 3 days (up to a maximum of 1 week) of the initial presentation. For patients who could not be contacted or were too ill to be interviewed or dead, proxy reporting was obtained from an immediate family member most familiar with the medical and contact history of the patients before infection. Data on case and contact information were collected on all 1755 SARS patients, although not all data elements were completed for all cases.

Laboratory confirmation of SARS was by: (1) reverse transcription–polymerase chain reaction (RT-PCR) for SARS-CoV and (2) serological testing for IgG against SARS-CoV. Patients were considered to have laboratory-confirmed SARS if there was: (1) a positive RT-PCR result from two or more clinical specimens, either from different sites or tested in different laboratories, obtained either from live patients or post-mortem; or (2) seroconversion by

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RFCID project number: HKU-AA-001

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ELISA, immunofluorescence assay (IFA) or neutralisation assay. Paired samples for serological testing were collected at least 21 to 28 days apart. All specimens were carried out in three designated laboratories (The Chinese University of Hong Kong, The University of Hong Kong, and the Department of Health) where rigorous quality control procedures were in place.

Statistical analysis

The epidemic time series of all 1755 local cases was constructed based on the date of symptom onset and infection cluster. Infection clusters were classified by probable transmission setting (institutional vs community), location (eg housing estates), occupation (eg health care workers) and workplace (eg hospitals). The age and sex distributions of SARS patients were compared with general population estimates derived from the 2001 population census.

To illustrate the geospatial pattern of disease spread, we used a geographic information system (ArcGIS and its extension modules) to construct a map of infection clusters in different districts of Hong Kong.

Empirical distributions were plotted for intervals from onset to admission, onset to death, and onset to discharge, and the mean and variance of these distributions calculated. The database contained 81 patients with one exposure to a confirmed SARS patient within 15 days (with start and end dates recorded), no travel and who were not hospitalised prior to the onset of symptoms. The relationship between the onset-to-discharge interval and patient age was tested by linear regression. A model was fitted to the onset-to-admission interval, with onset category as the independent variable. In addition, the sex-specific linear relationships between age and the variability of the onset-to-discharge and onset-to-death intervals were examined by modelling the standard deviation as a linear function in age. The resulting model was solved by the maximum likelihood method.

Logistic regression was used to identify factors significantly associated with fatality due to SARS. The following variables were tested in the model: age, sex, occupation (health care worker vs others), symptoms on presentation (typical vs atypical), infection cluster, calendar period of infection (as defined by the symptom onset date, interval from onset to admission), presence of pre-existing co-morbidities (including asthma, chronic obstructive pulmonary disease, cardiovascular disease, cerebrovascular disease, cancer, diabetes mellitus, chronic renal disease, and chronic liver disease). The ratio of the lactate dehydrogenase level to the upper normal limit was used as an indicator of disease severity on admission, and the number of days between the onset of symptoms and initiation of ribavirin. We used indicator variables to denote missing items for variables that did not have complete data coverage, ie atypical symptoms, infection cluster, and lactate dehydrogenase level.

Probability of survival/mortality curves were plotted (stratified by age) to illustrate the dependence of time-to-death for those who died. All analyses were repeated on the 1467 patients with laboratory confirmation of SARS. All statistical analyses were carried out on STATA version 8.0.

Results

Laboratory confirmation of SARS status

Of the 1755 SARS patients, 1467 (83.6%) were confirmed by laboratory: 447 seroconverted and had two or more positive RT-PCR results, 959 seroconverted only, and 61 had two or more positive RT-PCR results only. In 288 patients, laboratory confirmation was not possible for various reasons, including inadequate or insufficient specimens (n=199), negative RT-PCR and/or serology results (n=89).

Time

The patient who initiated the largest transmission chain in Hong Kong and the global outbreak was from Guangdong province. He first had symptoms on 15 February 2003 and was admitted to hospital on 22 February 2003, one day after arriving in Hong Kong.[4] The development of the epidemic featured a period of exponential growth, beginning on 10 March 2003, which was further exacerbated by transmission not related to intimate personal contact (in the Amoy Gardens estate and immediate neighbourhood).[4] This was followed by a period of comparative stability throughout early to mid April, with a declining trend beginning in the week of 22 April 2003. The last case had symptoms onset on 31 May 2003 and was admitted to hospital on 2 June 2003.

Place

About 49% of SARS patients were infected in clinics, hospitals or elderly/nursing homes. The superspreading event in Amoy Gardens resulted in a daily incidence of close to 100 at the height of the outbreak in late March. Spread within residential buildings accounted for 22% of all cases, mostly at Amoy Gardens. An additional 7% of all cases were classified as 'near to Amoy Gardens'. This referred to SARS patients living in the immediate neighbourhood of Amoy Gardens, who were believed to be linked to the main Amoy Gardens cluster, but not themselves residents of that housing estate. About 5% of Hong Kong cases were imported (or re-imported) from overseas or from air travel. Fewer than 10% resulted from transmission in the general community including household settings (aside from the superspreading event in Amoy Gardens). Of these, 64% (97/152) could be attributed to intra-familial or within-household spread (defined as transmission from one household or family member to another with no other known sources of an infectious contact).

There was clear clustering of cases in certain districts of the Kowloon peninsula (Kwun Tong in which Amoy Gardens is located) and the New Territories (Shatin and Tai Po districts where the Prince of Wales and Alice Ho

Mui Ling Nethersole Hospitals, sites of large nosocomial outbreaks, are located respectively), but Hong Kong Island was relatively spared. Clustering became apparent as the epidemic unfolded, with per capita incidence varying significantly between districts.[3]

People
The female/male ratio among infected patients was 1.26. Compared to the age and sex distribution of the Hong Kong general population, there was a clear excess of young adults, especially females (102 out of the 254 female SARS patients aged 25 to 34 years were nurses). Moreover, there was a relative deficit of children and adolescents. Elderly men (>75 years old) were over-represented among SARS patients, as were elderly women despite to a lesser extent. Health care workers accounted for 23% of all infected persons; most of them worked in the public sector, where SARS patients were mainly cared for (in 14 designated centres). Some patients were initially admitted to other hospitals but later transferred. Nurses accounted for 52% of the 405 health care workers infected, followed by health care assistants such as orderlies (28%) and medical doctors (16%).

Key epidemiological parameters
The estimated mean and variance of the incubation period was 4.6 and 15.9 days, respectively[2]; 95% of patients had the onset of symptoms within 12.5 days of infection.

Onset and admission times are both observable events. Patients were grouped by the week of clinical onset, and 11 time-periods were analysed. There were too few patients with symptom onset before 15 February 2003 for robust analysis. According to a biphasic linear model, the interval from symptom onset to admission decreased significantly during the first 5 weeks (P<0.001), but not over the last 6 weeks (P=0.27).

The respective mean and variance of the interval from symptom onset to death were 23.7 and 221.0 days, and for the interval from symptom onset to discharge were 26.5 and 194.9 days.[2] There was substantial variability in the distribution of these two intervals, with greater variance observed for the former. The variability decreased with age for the former (P=0.027), whereas the opposite was true for the latter (P<0.001). The symptom onset-to-death intervals varied significantly according to patient age, demonstrating an inverted U-shaped relationship, where those aged 50 to 59 years (especially females) had the longest mean intervals and those aged >70 years had comparatively briefer periods of illness before death. In contrast, older patients who survived were usually discharged later and this relationship appeared to be linearly related to age (P<0.001).

Case fatality ratios and associated predictors
The overall case fatality ratio was 17% (299 deaths out of 1755 SARS cases). Survival was heavily influenced by both age and sex. Male SARS patients had a 50% (95% CI=7-109%) excess risk of death. Mortality increased significantly with age (P<0.001). For example, none of the female patients <30 years old died, compared to approximately 75% of males aged >70 years died. A lower case fatality was associated with health care worker status (adjusted odds ratio [OR]=0.35; 95% CI, 0.15-0.80). The minority of individuals presenting with atypical symptoms (3%) had a significantly increased risk of death (adjusted OR=2.62; 95% CI, 1.24-5.53). Similarly, the presence of pre-existing co-morbidities and greater disease severity (as inferred from higher lactate dehydrogenase levels on admission) increased the risk of death. The calendar time-period during which patients fell ill was not significantly associated with survival, nor was earlier admission after the symptom onset, or the timing of ribavirin administration. The precise infection cluster that a patient belonged to was not a significant predictor (at the 0.05 level).

Analyses based on the subset of 1467 patients with laboratory confirmation of SARS produced similar results to those of the full cohort. However, health care worker status (adjusted OR=0.64; 95% CI, 0.26-1.56) and atypical symptoms (adjusted OR=2.06; 95% CI, 0.83-5.11) were no longer significantly associated with survival at the 0.05 level for this subset of patients. We believe that the full 1755 cohort should remain the main results partly because 199 out of 288 non-laboratory confirmed cases did not have adequate or sufficient clinical specimens to be tested. Nonetheless, they fulfilled clinical and epidemiological criteria for the diagnosis of SARS prior to laboratory testing. This is different from the scenario where results of both RT-PCR and serological tests were negative. Additionally, we examined the influence of missing data on the stability of the logistic regression models (ie both the 1755 and 1467 models) through a series of sensitivity analyses. The two variables with the most numbers of missing values, namely atypical symptoms (missing items=273, 16%) and lactate dehydrogenase level on admission (missing items=242, 14%), were excluded from the regression model. The results were robust even after deletion of these two variables, as they achieved significance as well as directionality and magnitude of associations. Moreover, after multiple imputation to deal with missing data for these two variables, the regression results were again very similar to the baseline model.

Discussion

Our findings provide a summary of the time-course and patient location of the 2003 Hong Kong SARS outbreak and the characteristics of those infected. The time-course of the epidemic was marked by an initial period of exponential growth and a decline after 6 weeks of intensive public health control measures. Significant geospatial clustering was observed, with several large clusters of SARS cases in hospitals and residential settings and a high proportion of health care workers. These observations are largely consistent with those reported for the Singapore

and Toronto outbreaks, where the hospital environment substantially amplified the risk of infection.[5-7] The pattern of infection clusters also suggests that the viral infection is of low transmissibility, except in settings of intimate contact or where significant environmental contamination occurred. It may also suggest low infectivity for some days following the onset of clinical symptoms. In addition, the risk of acquiring the infection varied significantly according to age, with relatively few cases and no deaths in children and adolescents. The reasons for this remain unclear.

One of the key aspects of infection control introduced during the epidemic was a policy of quarantine, where individuals who were possibly infected or had contact with known SARS cases were isolated for a fixed period. Definition of this period was informed by timely estimates of the time from exposure to first symptoms, ie the incubation period distribution. The analyses of the full dataset indicated that 13 days may be necessary to capture 95% of all possible cases,[2,8] compared to a period of 10 days recommended by the World Health Organization and US Centers for Disease Control and Prevention. Yet our estimation procedure adopted a parametric gamma distribution and thus implicitly assumed the possibility of very long incubation periods. In addition, owing to methodological constraints, this distribution was fitted to data on a very small subset of cases with a single exposure source with known start and end dates, and therefore the generalisability of these findings to the whole sample was unknown.

The analysis of the onset-to-admission interval showed a progressive shortening of the interval from the onset of symptoms to presentation at hospital, likely due to heightened community awareness and a high index of suspicion among health care providers as the epidemic spread.[9] Coupled with the observation that SARS almost exclusively manifested as a florid clinical syndrome requiring inpatient treatment and rarely as a subclinical or mild infection (ie with no asymptomatic carriers of the disease), it was possible to reduce the onset-to-admission interval to a minimum (ie 2 days) and this might be an effective public health control measure. It was relatively easy for those infected to recognise their illness and promptly present to the health care system. This enabled rapid isolation of infectious individuals, hence reducing the effective infectious period and thus the risk of onward transmission. However, shortening the time between first symptoms and the initiation of treatment after hospital admission did not appear to increase the probability of survival. Clinical studies of the typical course of infection in SARS-CoV patients suggested that the average peak infectiousness may occur 8 to 9 days after the onset of symptoms.[10] This pattern, which is atypical for most respiratory or gastrointestinal tract infections, implies that prompt isolation after the onset of symptoms is a very effective public health measure for this particular infection. This observation also helps to explain the large fraction of cases that occurred in health care workers in Hong Kong, Singapore, Taipei and Toronto, since they had contact with

patients during their peak infectious phase.

The distributions of onset-to-death and onset-to-discharge intervals add information to the natural history of the disease process (mostly among treated patients) and underline the importance of patient age and sex in determining the course of illness. They also allow clinicians to understand the relative distributions of time to clinical outcomes, so that this SARS outbreak can be compared to future outbreaks should they occur. The lower mean and variability in the symptom onset-to-death interval distribution among the deceased elderly was likely due to their relative frailty and higher prevalence of co-morbidities. Whereas factors such as post-SARS disability and treatment complications might have led to a longer hospital stay for elderly survivors; some of these patients were hospitalised for treatment of other diseases after recovery from SARS. The modal peak of the symptom onset-to-discharge interval distribution of 21 days was, to an extent, an artefact of administrative guidelines, namely a minimum 21 days of hospitalisation, which had been in effect since early April 2003.

The estimation of epidemiological parameters and case fatality ratios during an ongoing epidemic is complicated by the open cohort problem of censoring, such that it is impossible to ascertain who will eventually die or be discharged among those still hospitalised at the time of the analysis. This is further complicated by the temporal evolution of the epidemic with incident cases continually being added to the pool of infected individuals. In this analysis of all 1755 consecutive cases in Hong Kong, the outcome was observed in all cases and hence issues regarding censoring do not apply.

Although the overall case fatality ratio was 17%, this figure masks the significant variation in case fatality by age. Male gender, more severe illness on presentation as indicated by the lactate dehydrogenase level, and the presence of pre-existing co-morbidities were significantly associated with a high case fatality in the multivariable analysis. The timing of ribavirin administration did not significantly influence clinical outcome, possibly due to residual confounding or insufficient power to detect a difference given that most patients were treated. Previous analyses of case fatality predictors have only examined small, hospital-based datasets with limited information on a comprehensive range of personal and clinical variables, yet their findings were similar to the present study with respect to the effects of age, sex, co-morbidities and high lactate dehydrogenase levels on mortality. It should be noted that even in the largest case cohort in Hong Kong, there was insufficient statistical power to examine all important factors that might have influenced case fatality.

As our study demonstrated, the appropriate methodology to identify predictors of survival (or case fatality) is through a multivariable logistic regression model with a closed cohort. In the heat of a crisis, however, observational studies based

on amalgamated datasets from different clinical settings are the only means by which treatment value can be assessed. In drawing conclusions from such analyses, bias may be present in patient choice for any given treatment, and this must be taken into account.

Conclusions

Future research should closely examine the relative merits and drawbacks of different statistical approaches to estimating the distribution of incubation periods, since such estimates are central to public health and evolving an infection control policy. Quarantine times must take into account the extent of potential disruption to people's lives and the likely degree of compliance in different communities.

To clarify some of the unresolved issues raised in this report, more detailed analysis involving other relevant clinical factors, such recourse to non-invasive assisted ventilation or other medications and their timing, as well as longitudinal observations of clinical and laboratory parameters are needed.

Public health authorities worldwide should formulate appropriately resourced protocols for randomised controlled trials to properly evaluate the efficacy of various management strategies should SARS recur. While SARS is unlikely to return as a large epidemic across many different countries, clinical investigators need to recognise the importance of multi-national, multi-centred epidemiological studies and collaboration. This should extend to clinical trials to increase the power to detect moderate effects of treatment regimens and associated risk factors.

Acknowledgements

References

1. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003;362:1353-8.
2. Department of Communicable Disease Surveillance and Response, World Health Organization. Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). Geneva: World Health Organization; 2003.
3. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003;361:1761-6.
4. SARS Expert Committee. SARS in Hong Kong: from experience to action. Hong Kong: HKSAR Government; 2003.
5. Leung GM, Rainer TH, Lau FL, et al. A clinical prediction rule for diagnosing severe acute respiratory syndrome in the emergency department. Ann Intern Med 2004;141:333-42.
6. Lipsitch M, Cohen T, Cooper B, et al. Transmission dynamics and control of severe acute respiratory syndrome. Science 2003;300:1966-70.
7. World Health Organization. Summary of probable SARS cases with onset of illness from November 1, 2002 to July 31, 2003. WHO website: http://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed 26 May 2004.
8. Public health guidance for community-level preparedness and response to Severe Acute Respiratory Syndrome (SARS) Version 2 Supplement D: Community containment measures, including non-hospital isolation and quarantine. US Centers for Disease Control and Prevention website: http://www.cdc.gov/ncidod/sars/guidance/D/index.htm. Accessed 14 Feb 2004.
9. Leung GM, Lam TH, Ho LM, et al. The impact of community psychological responses on outbreak control for severe acute respiratory syndrome in Hong Kong. J Epidemiol Community Health 2003;57:857-63. Erratum in: J Epidemiol Community Health 2003;57:995.
10. Peiris JS, Chu CM, Cheng VC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767-72.