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Research

SARS Transmission, Risk Factors, and Prevention in Hong Kong

Joseph T.F. Lau,* Hiyi Tsui,* Mason Lau,* and Xilin Yang*
*Chinese University of Hong Kong, Hong Kong, China

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We analyzed information obtained from 1,192 patients with probable severe acute respiratory syndrome (SARS) reported in Hong Kong. Among them, 26.6% were hospital workers, 16.1% were household members of SARS patients and had probable secondary infections, 14.3% were Amoy Garden residents, 4.9% were inpatients, and 20.1% were contacts of SARS patients who were not family members. The remaining 347 case-patients (29.1%) did not have "known" sources of infection. Excluding those <16 years of age, 330 patients with cases from "undefined" sources were used in a 1:2 matched case-control study. Multivariate analysis of this case-control study showed that having visited mainland China, hospitals, or the Amoy Gardens were risk factors (odds ratio [OR] 1.95 to 7.63). In addition, frequent mask use in public venues, frequent hand washing, and disinfecting the living quarters were significant protective factors (OR 0.36 to 0.58). In Hong Kong, therefore, community-acquired infection did not make up most transmissions, and public health measures have contributed substantially to the control of the SARS epidemic.

As of June 11, 2003, a total of 1,755 probable SARS cases were reported in Hong Kong (1). Some of the sources of SARS transmission are unknown. For instance, the first major SARS outbreak occurred in the Prince of Wales Hospital in March 2003, and 138 probable cases were reported from March 11 to March 25, 2003 (2). Another major outbreak occurred in the Amoy Gardens housing estate on approximately March 26, 2003, and a total of 321 residents were affected (3). A total of 381 hospital workers were affected as of May 29, 2003 (4). Other sources of infection are possible. Some inpatients were cross-infected by SARS case-patients, who were hospitalized for reasons other than SARS; others may have contracted the disease through known contacts with other SARS patients. The rest of the community-acquired case-patients contracted the diseases through less defined sources. The distributions of the "known" and "undefined" sources of infection have not been reported. Such an initiative would help assess the infectivity and modes of transmission of the virus in the community setting.

Also, reports that public health measures, such as wearing masks, frequent hand washing, avoidance of crowded places, disinfection of the living quarters had been practiced by most of the Hong Kong population during the SARS outbreak (>90%) (5). The efficacy of widespread use of masks was controversial (6), and evaluating the efficacy of such measures in controlling the epidemic is important.

Our study had two objectives. First, we sought to delineate the distribution of different sources of transmission of the SARS cases in Hong Kong. The number of cases with known and undefined sources was determined. Patients with known sources included those who were hospital workers, those who lived in the Amoy Gardens Estate, those who were probable secondary cases within a household (i.e., those with another household member who had SARS with an earlier date of onset), those who were inpatients and were cross-infected by other inpatients, and those persons who had contact with another SARS patient (who was not one of their household members) before the onset of fever. For the remaining cases, the virus was contracted through undefined sources.

The second objective was to identify the undefined source group. A number of hypotheses were tested to identify relevant risk and protective factors associated with contracting the disease. Risk

factors were related to visiting places of potentially high risk and meeting at-risk people. Preventive factors were related to public health measures for prevention.

Methods

The study population comprised all probable SARS patients whose cases were reported to the Department of Health on or before May 16, 2003 (n = 1,690). The SARS case definition criteria for SARS cases, used by Hong Kong Hospital Authority, is as follows: radiographic evidence of infiltrates consistent with pneumonia and current temperature >38°C or a history of such at any time in the preceding 2 days, and at least two of the following: history of chills in the past 2 days, new or increased cough, breathing difficulty, general malaise or myalgia, typical signs of consolidation, and known exposure. These criteria for cases are equivalent to those in the World Health Organization's case definition for probable SARS cases (7).

Data Collection

Telephone numbers, as well as some demographic and clinical background information, for all probable SARS case-patients in Hong Kong (identified on or before May 16, 2003 [n = 1,690]) were obtained from the Department of Health. A team of trained interviewers called all these numbers, briefed the person answering the phone about the nature of the study, and invited their household to join the study. Informed consent was obtained directly from the respondents. The number of SARS patients in the household was ascertained, and the interviewer identified the index patient, the person who had the earliest date of onset of fever if the household had more than one SARS patient. The rest of the SARS patients, those with later onset of illness, were considered as having probable secondary or tertiary cases. When a household had had two or more SARS patients with the same fever onset date (11 households), both were treated as index patients rather than as having probable secondary cases. The information obtained was cross-checked with that obtained from the SARS registry. Ethics approval was obtained from the Ethics Committee of the Chinese University of Hong Kong.

The study was conducted from April 4, 2003, through June 10, 2003. Of the 1,690 probable SARS case-patients reported in Hong Kong as of May 16, a total of 1,214 (72%) SARS case-patients from 996 households were covered by our study. Of the remaining 476 case-patients not covered by this study, 140 case-patients (8.2%) did not have a correct telephone number, 163 (9.6%) could not be contacted after at least five attempts, 163 (9.6%) declined to participate, and 10 (0.6%) were either not in Hong Kong or could not communicate in Chinese or English.

Study Design

The study is part of a project that also includes an investigation of the secondary attack rate of household members. For the first part of this study, the index case-patients were asked whether they were hospital workers, inpatients before contracting SARS, or residents of the Amoy Gardens. The other respondents were asked whether onset of fever occurred within 10 days of contact with a SARS patient. These four types of SARS cases were classified into the known sources group. The rest of the index case-patients were classified into the undefined source group. In the second part of the study, a 1:2 matched case-control study was conducted for the undefined source group to identify risk and preventive factors associated with SARS transmission in the community setting.

Adults >16 years of age were included in the case-control study (17 case-patients were removed from the analysis). Potential geographically related risk factors studied included whether the case-patient had visited (but not lived in) Amoy Gardens, Prince of Wales Hospital, other hospitals or clinics, or crowded places within 10 days before onset of fever. Other risk factors were related to contact with other groups of people during the same reference period, including medical personnel, hospital visitors, and persons with influenzalike symptoms (who were not SARS case-patients). A number of protective factors were related to relevant public health measures, including the frequency of using a face mask in public venues, the frequency of washing hands each day, and disinfection of living quarters thoroughly during the same period. The same questions were asked to the control group, which was recruited by a random telephone survey. Members of the control group were matched for age and sex with the case-patient.

The reference period was the same as that of the matched case-patient. Random telephone numbers were selected from up-to-date local telephone directories. Interviews were conducted in the evening to avoid overrepresenting those who were not working during the daytime. At least three calls were made before an unanswered call was considered as a noncontact. Informed consent was obtained before the interviews were conducted. Almost all case-patients were interviewed within 14 to 28 days after their onset of fever, and the control group was interviewed accordingly. When a participant was unable to answer the questionnaire, a proxy, who was most familiar with the family situation, was interviewed.

Data Analyses

For the case-control study, odds ratios (OR) were first examined by using univariate logistic regression models. The significant univariate variables were then entered as input for the multivariate forward conditional logistic regression analysis; p values <0.05 were statistically significant. SPSS for Windows Release 11.0.1 (SPSS Inc., Chicago, IL) was used to analyze the data.

Results

Cases with Known Sources of Transmission

Of the 1,214 probable SARS cases covered by this study, 22 questionnaires (1.8%) were incomplete and did not allow us to classify the respondents into groups according to source of transmission. The rest (n = 1,192) were analyzed. A total of 192 (16.1%) had probable cases of secondary or tertiary household transmission (Table 1) (i.e., another household member had SARS but fever onset occurred earlier). All the names were verified as being reported to the SARS registry. Another 317 of 1,192 (26.6%) cases were hospital workers; 170 (14.3%) lived in the Amoy Gardens; 58 (4.9%) were inpatients who had been hospitalized for diseases other than SARS and kept on wards with SARS patients. Most infected inpatients were long-term chronic patients and had been hospitalized for >2 weeks before having SARS symptoms. These patients were likely to have been cross-infected. A total of 727 case-patients belonged in one of the four categories (61% of 1,192 cases). Another 240 (20.1%) had come into contact with a SARS patient within a 10-day period before onset of fever. For 347 (29.1%) participants, the source was undefined; these participants were included in the case-control analysis. After excluding 17 case-patients ≤16 years of age, 330 participants were included in the case-control study.

Univariate Case-Control Analysis

Of the 330 patients with an undefined source of infection, 48% were men and 52% were women. The mean age of the patient group was 47.1 years for both the male and female case-patients (standard deviation [SD] 18.8 and 19.9, respectively, $p > 0.05$, t test). The percentage of participants in the undefined source group in the three periods of the epidemic (before March 25, 2003, from March 26 through April 10, and after April 10) were 24.2%, 36.1%, and 43.5%, respectively.

Members of the patient group were more likely than the control group to have visited mainland China (12.7% vs. 6.5%, $p < 0.005$). One patient had visited Taiwan, another patient had visited Singapore, two controls had visited Taiwan, and none of the controls had visited Singapore (Singapore and Taiwan were listed as affected areas during the study period). Similarly, patients were also more likely than controls to have visited the Amoy Gardens (15% vs. 2%, OR = 9.10, $p < 0.005$) (keeping in mind that those who lived in the Amoy Gardens had already been removed from the analysis); patients were more likely than the controls to have visited the Prince of Wales Hospital (3.6% vs. 0.5%, OR = 8.27, $p < 0.005$) or other hospitals or clinics (40.7% vs. 17.0%, OR = 3.36, $p < 0.005$) (Table 2). A total of 212 cases of the undefined source group had visited at least one of the above-mentioned categories of places. Frequency of visiting crowded places was, however, not significant in the univariate analysis (21.91% vs. 20.8%, OR = 1.07, $p > 0.05$).

Members of the case-patient and control groups were not statistically different in the percentage of having come into contact with someone with influenzalike symptoms (those having made contacts with SARS patients were already removed, 9.0% vs. 6.4%, OR = 1.42, $p > 0.05$). The two groups were also not different in the likelihood of having social contact with someone who had visited a hospital (8.2% vs. 5.2%, OR = 1.66, $p > 0.05$) or having social contact with medical personnel (7.6% vs. 8.6%, OR = 0.87, $p > 0.05$). Also patients were not more likely to have a known SARS patient living in the same housing estate, after Amoy Gardens patients had already been removed from the analysis (such data were made available to the public by the government after April 12, 2003) (8).

Furthermore, matching for the reference period, members of the case group were less likely than members of the control group to have frequently worn a face mask in public venues (27.9% vs. 58.7%, OR = 0.36, $p < 0.005$), to have been washed their hands >10 times a day (18.4% vs. 33.7% OR = 0.44, $p < 0.005$), and to have disinfected their living quarters thoroughly (46.6% vs. 74.5%, OR = 0.30, $p < 0.005$).

Multivariate Analysis

When all the variables that were significant in the univariate analysis were used as input for the multivariate stepwise conditional logistic regression analysis, the results show that among the 330 patients with undefined sources, the following were significant risk factors: having visited mainland

China (OR = 1.95, p = 0.020, Table 2), having visited the Amoy Gardens (OR = 7.63. p < 0.001), having visited the Prince of Wales Hospital (OR = 7.07, p = 0.009), and having visited other hospitals or clinics (OR = 3.70, p < 0.001) during the reference period. On the other hand, using a mask frequently in public places (OR = 0.27, p < 0.001), washing one's hands >10 times a day (OR = 0.58, p = 0.008), and disinfecting the living quarters thoroughly (OR = 0.41, p < 0.001) during the reference period were significant protective factors (Table 2).

Undefined Cases

After removing those case-patients who may have contracted SARS after visiting the Amoy Gardens, the Prince of Wales Hospital, other hospitals, or an affected country, including mainland China, Singapore, and Taiwan (212 cases of the 330 cases), 118 cases remained undefined. They were likely to be community-acquired cases of unknown sources of transmission. When univariate and multivariate conditional logistic regression analyses were repeated for the 118 cases with undefined sources (after 212 patients who had visited some particular places that were associated with risk for transmission were removed from the analysis) and their controls (n = 226), similar results were obtained. The three public health variables—frequently wearing a mask in public places (adjusted OR = 0.36, p < 0.001), washing hands >10 times a day (adjusted OR = 0.44. p = 0.008), and disinfecting the living quarters thoroughly (adjusted OR = 0.36, p < 0.001)—remained significant protective factors. Again, similar to the results of the previous analysis applied to the 330 cases, the other five variables (visiting crowded places, having contact with someone with influenzalike symptoms, having social contact with hospital visitors, having social contact with medical workers, and living with in the same housing estate as other SARS case-patients) were not significant risk factors.

Discussion

Of the 1,192 participants in this study, approximately 16.1% had probable secondary or tertiary transmission occurring within the household, 26.6% were hospital workers with nosocomial infections, 14.3% were Amoy Gardens patients, and 4.9% were cross-infected inpatients. In 20.1%, SARS might have been contracted when the participant came in contact with a SARS patient who was a nonhousehold member, which may have occurred in a hospital or community setting. SARS may have developed in 17.8% after they visited Amoy Gardens, hospitals or clinics, or affected countries. This computation leaves 9.9% as community-acquired cases of an unknown source.

The percentage of patients related to Amoy Gardens (someone who lived there or visited there) is 18.5% (221/1,192). The percentage of patients with a hospital connection (hospital workers, inpatients, and visitors) is 44.5% (530/1,192). The proportion of unknown community-acquired SARS infection among all SARS cases in this study was considerably lower than the proportion of nosocomial infection, which suggests that preventing hospital outbreaks is essential.

Of the 330 undefined transmissions, 44.2% of the transmissions occurred through hospital visitors. Another study on household transmission also indicated that hospital visits were a significant risk factor for predicting household secondary infection (9). Therefore, the severity of future outbreaks, if any, would depend on the ability of the hospital system to control hospital cross-infection and infection of visitors.

Visits to mainland China were associated with SARS transmission, even after adjusting for other variables. Cross-border transmission played a role in the epidemic; although the absolute percentage is not high among the 1,192 case-patients (3.4% or 41/1,192), it is substantially larger among the undefined source group (13.03%). With a case-control design, we could not establish whether this 13.03% was associated with an inflated risk. Cross-border communication and prevention, such as those set in place (temperature screening and health declaration), need to be enforced strictly and consistently. Almost 70% of the 41 participants who visited mainland China had fever onset on or before April 1 (i.e., the early phase of the epidemic) (5). None of them had onset after May 3, which is understandable as visiting mainland China was perceived as a high risk by the general public in the late phase of the epidemic (5).

The variables related to social contacts (with medical personnel or hospital visitors, with persons with influenzalike symptoms, and with persons living in a housing estate with a reported SARS patient) were not significant. These findings should be interpreted with caution. On one hand, these case-patients should not be stigmatized. On the other, the results may have been confounded because all SARS cases contracted this way were excluded from the analysis. However, confirming that these variables could not account for transmission of the undefined source cases can be useful.

Evidence does not indicate that frequent visits to crowded places were associated with a higher likelihood of community-acquired infection. This finding may remove panic that arose during the epidemic, and daily life need not change as much as it had. Hong Kong is a densely populated city, and it had a large number of SARS cases. The number of community-acquired cases in less

populated cities should be much lower than that of Hong Kong. This finding should be interpreted with care as >90% of the general public wore face masks in public places, and >85% avoided visits to public places during the epidemic in Hong Kong (5). Although visiting the Amoy Gardens was a risk factor, Amoy Gardens might be the only place where such a large-scale SARS outbreak was attributable to contamination of the environment.

We now have some empirical evidence to suggest that wearing a face-mask frequently in public places, frequent handwashing, and disinfecting one's living quarter were effective public health measures to reduce the risk for transmission (adjusted OR 0.58 to 0.36). The effectiveness of mask use was controversial (6). In another study, the prevalence of these three public health preventive public health measures increased significantly from March 21, 2003, to April 1, 2003, (i.e., wearing masks 11.5%–84.3%; frequent hand washing 61.5%–95.1%; home disinfection 36.4%–80%) (5). These practices played an essential role in limiting the spread of the virus in the community in Hong Kong.

That disinfecting the living quarter is a strong protective factor has a particular relevance. The reason behind the significance is not completely clear. During the epidemic, the Hong Kong government released frequent announcements of public interest to promote home disinfection using 1:99 bleach water solutions. Most respondents who disinfected their living quarters were probably following the government's suggestion. Keeping in mind that probable secondary cases had already been removed from the analysis, such protective effect is not referring to the effects that disinfecting the quarter reduced the chance of secondary infection. Environmental contamination (suspected to be related to the sewage system) was reported in the Amoy Gardens, and similar environmental contamination probably did not occur in other places. Such contamination-related infections might be on a small scale and not been noticed. In such circumstances, home disinfection might reduce the risk for transmission. The finding suggests that, in addition to the droplet theory, the fomites theory could not be dismissed.

Our study has a few limitations as well as strengths. First, approximately 72% of all SARS case-patients were included in the study (excluding patients whose contact numbers were incorrect or not available; approximately 78% of those with a valid contact telephone number were included, and the refusal rate was about 10%). The sample size was reasonably large. Second, data were collected retrospectively. Most of the data were, however, collected from the participants within 1 month after onset of fever. Since contracting the disease is a major life event for the patient and family, they should be able to recall whether such factual and benchmark behaviors had been practiced.

The study also has strength of matching for age, sex, and reference time of the behaviors in question, so that both the case and control in a pair were referring to relevant behaviors that occurred within the same 10-day period before the date of onset of fever of the patient. Third, some questions, such as those about disinfection of households or visiting crowed places were nonspecific (the questions asked were "Whether your living quarter had been disinfected thoroughly" and "Whether you had visited crowded places"). Different participants might have defined the terms differently. Further, a number of patients were unable to answer the questions, and a household member who was "most familiar with the household situation" was invited to serve as a proxy. The responses obtained from these informants were compared to those obtained from the patients themselves, and no statistical significance was obtained ($p = 0.199$ to 0.854) to all variables, except the variable about visiting the Amoy Gardens ($p < 0.05$).

One particular strength of the study in its evaluation of the three public health measures is that transmissions due to various known sources of infection had been removed as much as possible. In conclusion, the study shows that public health measures may have contributed substantially to the control of SARS epidemic in Hong Kong.

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Dr. Lau is the director of the Center for Epidemiology and Biostatistics of the School of Public Health of the Chinese University of Hong Kong. His research interests include community research on behavioral aspects of infectious disease, such as HIV prevention studies.

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Table 1. Distribution of 1,214 severe acute respiratory syndrome cases covered by the study

	n	%
Incomplete information	22	-
Complete information	1,192	100[a]
Known sources (any of 1.1 to 1.4)	727	61.0
Probable secondary/tertiary household infection	192	16.1
Hospital care workers	317	26.6
Amoy Gardens residents	170	14.3
Inpatients	58	4.9
Not belong to 1.1-1.4 but had contacted SARS patient/s within 14 days before onset of fever	240	20.1
Patients with cases of undefined sources (do not belong to 1 and 2)	347	29.1
Visited Amoy Gardens[b]	51	4.3
Visited PWH[b]	12	1.0
Visited other hospitals or clinics[b]	134	11.2
Visited an affected country[b]	43	3.6
None of 3.1 to 3.4[b]	118	9.9

[a]Calculated based on complete data.

[b]Not including patients <16 years of age; PWH, Prince of Wales Hospital.

Table 2. Preventive measures and risk factors reported by cases and controls[a]

Factors	Case[b]	Control[c]	Matched univariate OR (95% CI)	Matched multivariate OR (95% CI)	p value[d]
% visited mainland China (reference=no)	12.7	6.5	2.09 (1.33 to 3.27)[e]	1.95 (1.11 to 3.42)	0.020
% visited PWH (reference=no)	3.6	0.5	8.27 (2.32 to 29.49)[e]	7.07 (1.62 to 30.75)	0.009
% visited other hospitals/clinics (reference=no)	40.7	17.0	3.36 (2.49 to 4.54)[e]	3.70 (2.54 to 5.39)	<0.001
% visited Amoy Gardens (reference=no)	15.5	2.0	9.10 (4.87 to 17.00)[e]	7.63 (3.77 to 15.43)	<0.001
% visited crowded places frequently (reference=occasionally/seldom/no)	21.9	20.8	1.07 (0.76 to 1.50) NS	-	-
% contacted someone with fever or influenza (reference=no)	9.0	6.4	1.42 (0.87 to 2.32)	-	-

			NS		
% social contact with someone who visited a patient in a hospital (reference=no)	8.2	5.2	1.66 (0.96 to 2.85) NS	-	-
% social contact with medical personnel (reference=no)	7.6	8.6	0.87 (0.52 to 1.44) NS	-	-
% had a SARS case in the housing estate (reference=no)	6.6	8.5	0.76 (0.44 to 1.31) NS	-	-
% disinfected the living quarters thoroughly (reference=no)	46.6	74.5	0.30 (0.23 to 0.39)[e]	0.41 (0.29 to 0.58)	<0.001
Wore a mask in public places frequently (reference=occasionally /seldom/no)	27.9	58.7	0.27 (0.20 to 0.37)[e]	0.36 (0.25 to 0.52)	<0.001
Washed hands 11 or more times per day (reference=1–10 times/day)	18.4	33.7	0.44 (0.31 to 0.63)[e]	0.58 (0.38 to 0.87)	0.008

[a]N.S., not significant; OR, odds ratio; CI, confidence interval; -, not used by the multivariate analyses. The reference time period was the 10 days before the date of the patient;|s onset of fever.

[b]n = 330.

[c]n = 660.

[d]p values for multivariate OR.

[e]p<0.005.

Comments to the Authors

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Joseph T.F. Lau, Centre for Epidemiology and Biostatistics 5/F, School of Public Health, Prince of Wales Hospital, Shatin, N.T., Hong Kong; fax: 852-2645-3098; email: jlau@cuhk.edu.hk

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SARS Transmission among Hospital Workers in Hong Kong

Joseph T.F. Lau,* Kitty S. Fung,* Tze Wai Wong,* Jean H. Kim,* Eric Wong,* Sydney Chung,* Deborah Ho,* Louis Y. Chan,* S.F. Lui,† and Augustine Cheng*

Despite infection control measures, breakthrough transmission of severe acute respiratory syndrome (SARS) occurred for many hospital workers in Hong Kong. We conducted a case-control study of 72 hospital workers with SARS and 144 matched controls. Inconsistent use of goggles, gowns, gloves, and caps was associated with a higher risk for SARS infection (unadjusted odds ratio 2.42 to 20.54, $p < 0.05$). The likelihood of SARS infection was strongly associated with the amount of personal protection equipment perceived to be inadequate, having <2 hours of infection control training, and not understanding infection control procedures. No significant differences existed between the case and control groups in the proportion of workers who performed high-risk procedures, reported minor protection equipment problems, or had social contact with SARS-infected persons. Perceived inadequacy of personal protection equipment supply, infection control training <2 hours, and inconsistent use of personal protection equipment when in contact with SARS patients were significant independent risk factors for SARS infection.

The first large-scale outbreak of severe acute respiratory syndrome (SARS) occurred on or near March 12, 2003 in the Prince of Wales Hospital in Hong Kong (1). In this worldwide epidemic, hospital workers were one of the affected groups; as of May 31, 2003, a total of 384 (22.1%) of 1,739 suspected or confirmed cases reported in Hong Kong were hospital workers (2). In the initial phase of the epidemic, hospital workers did not take special protective measures. Thus, hospital workers accounted for 43.6% (68 of 156 cases) of those admitted to the Prince of Wales Hospital from March 11 to 25, 2003 (3). By May 25, 2003, a total of 453 confirmed SARS cases had been admitted to hospitals in the New Territories East cluster of the Hospital Authority in Hong Kong, which serves 1.3 million people and to which the Prince of Wales Hospital belongs. From March 28, 2003, to May 29, 2003, a total of 77 cases of SARS infection among hospital workers had been reported by the 5 hospitals in the cluster.

A recent study concluded that the use of protective masks is an effective countermeasure against SARS (4). Nevertheless, even after these measures were implemented, there were approximately 300 more hospital workers in whom the disease developed. Limitations of that study were the small number of cases and potential confounding by the possible differences in the intensity of care given to the SARS patients between the case and control groups.

Breakthrough transmission continues despite implementing strict infection control measures. We investigated the factors associated with breakthrough transmission of the SARS virus among hospital workers infected in hospital settings.

Materials and Methods

Study Design

A 1:2 matched case-control design was used. All participants were working in wards with SARS inpatients, some of which also included non-SARS patients. The case group included all infected hospital workers in the five hospitals of the New Territories East cluster of the Hospital Authority in Hong Kong who were registered as SARS cases by the Department of Health's eSARS registry and were hospitalized during March 28 through May 25, 2003.

The SARS case definition criteria used by Hong Kong Hospital Authority is as follows: radiographic evidence of infiltrates consistent with pneumonia, and current fever >38°C or a history of such at any time in the preceding 2 days, and at least two of the following: history of chills in the past 2 days, new or increased cough or breathing difficulty, general malaise or myalgia, typical signs of consolidation, or known exposure. These criteria are equivalent with the World Health Organization's case definition for probable SARS. Suspected SARS cases are those that do not completely fulfill the above definition

*Chinese University of Hong Kong, Special Administrative Region, People's Republic of China (SAR); and †Hospital Authority, Government of Hong Kong, Hong Kong SAR

but were considered to be likely cases of SARS on the basis of clinical judgment. If no known history of exposure exists, patients are considered for exclusion if an alternative diagnosis can fully explain the clinical symptoms. Laboratory confirmation of SARS infection was also conducted by one or more of the following assays: reverse transcriptase-polymerase chain reaction (RT-PCR); culture from throat wash, urine, stool and nasal swab specimens taken at days 1, 3, and 5; or paired serologic assay from clotted blood taken at day 1 and 21.

Of 77 probable and suspected SARS cases, 72 (93.5%) participated in the study. As all staff was required to use protective masks from March 12, 2003, these hospital workers were presumed to have contracted the virus as a result of breakthrough transmission. An infection control nurse explained the purpose and logistics of the study to the study participants, obtained their verbal consent for participation, presented them with a structured questionnaire, and collected the completed questionnaire. SARS case-patients were asked to nominate as controls two colleagues who had been working in the same job position, in the same ward, and in proximity with the case-patient before he became ill. Medical and nursing staff (48 of 72 cases) self-administered the questionnaires while other staff (e.g., healthcare assistants and ward assistants) were interviewed by an infection control nurse. Out of the 72 cases, 57 nominated 114 controls who completed the questionnaire (114/144 = 79.2%); 15 cases did not nominate a control and hence 30 controls were randomly selected from the duty roster of the day before the case felt unwell, matching for job position (30/144 = 20.8%). Questionnaires were collected from 57 (79.2%) nominated controls. Nominated controls who did not return the questionnaire were replaced by controls randomly selected from the duty roster of the day before the case felt unwell, matching for job position (15/72 = 20.8%). Of the 144 controls completing the questionnaire, one was invalidated because she later became a suspected case. Controls showed neither influenzalike symptoms nor SARS-related symptoms during the study and had not been identified as a suspected SARS case as of August 15, 2003. No blood test was conducted to determine whether these persons were asymptomatic SARS cases. Another study that tested 674 healthcare workers who were working in the same hospital cluster found no asymptomatic or subclinical SARS. It can thereby be assumed that the control group had not contracted the virus (5).

Measurements

Questions were asked about the hospital worker's job position, whether the healthcare worker had been seconded from another unit, whether he/she had made physical contact with any SARS patients and if so, whether various high-risk procedures were performed to the SARS patient (including intubation, suction, cardiopulmonary resuscitation).

Personal protection equipment use (N95 mask, surgical mask, gloves, goggles, gown, and cap) was examined under three different settings: when having direct contact with SARS patients, when having contact with "patients in general" (includes both SARS and non-SARS patients), and when there was "no patient contact." Information about the frequency of using different types of personal protection equipment (never, occasionally, most of the time, or all of the time) was asked for each of these three settings. A respondent was considered to be exposed to a particular risk if he or she had "never" or "occasionally" been using personal protection equipment rather than "most or all of the time." Those who had not been in contact with any SARS patients or patients in general were considered as not having been exposed to the particular risk. Respondents were asked whether they perceived the supply of such personal protection equipment items to be adequate or not (yes/no). Questions regarding the frequency of hand washing after making contact with SARS patients, patients in general and when there was no patient contact (never, occasionally, most of the time, all of the time) were also asked. In the analysis, frequency of using personal protection equipment and frequency of hand hygiene practice were coded into 2 categories: used inconsistently (i.e., "never or occasionally used") or used consistently ("used most or all of the time").

Study participants were also asked to assess whether the masks fit them (yes/no), whether their goggles were fogged (yes/no), and the frequency of touching protective masks (never, occasionally, most of the time, or always), and whether they had any problems complying with infection control procedures (yes/no). Respondents were asked whether they had ever made social contact with others who were later found to be SARS case-patients before SARS-related symptoms manifested (yes/no/not sure), within the 14-day period before the case's onset of symptoms. The questionnaire also asked about the respondent's exposure to infection control training (length of SARS infection control training) and whether they understood the infection control measures (yes/no). A trained research assistant contacted the respondents by telephone to follow up on any incomplete or unclear answers.

Statistical Methods

Unadjusted matched odds ratios calculated from conditional logistic regression methods (6) are summarized in Tables 1 to 4. A multivariate conditional logistic regression was fitted using a forward-stepwise procedure with all variables that were marginally significant ($p < 0.10$) in the unadjusted analyses as candidates for selection. Matched odds ratios and their exact 95% confidence intervals were

derived. LogXact for Windows version 4.1 was used for all calculations (7).

Results

Background Characteristics of Respondents

The 72 SARS-infected healthcare workers worked in five hospitals (distribution: 50% Alice Ho Miu Ling Nethersole Hospital, 40.3% from Prince of Wales Hospital, 2.8% from North District Hospital, 4.2% from Shatin Hospital, and 2.8% from Taipo Hospital). The study sample was composed of nurses 59.7% (n = 43), healthcare assistants 23.6% (n = 17), medical officers 9.7% (n = 8), clerical staff (2.8%, n = 2), and workmen (4.2%, n = 3).

Use of Masks and Other Types of Protection Equipment

Almost 100% of the study respondents used either an N95 mask or surgical mask in all 3 settings (Table 1). The differences of the use of the N95 mask (most of those not

Table 1. Percentage of healthcare workers exposed to the risk of inconsistent use of different types of personal protection equipment in 3 clinical settings with SARS patients[a]

Type of personal protection equipment	Controls (n = 143)	%	Case-patients (n = 72)	%	Matched OR (exact 95% CI)	p value (exact)
N95 or Surgical mask[b]						
Direct contact with SARS patient	0	0	1	1.4	2.00 (0.05 to ∞)	0.6667
Direct contact with patients in general[c]	1	0.7	2	2.8	4.00 (0.21to 235.99)	0.5185
No patient contact[d]	3	2.2	4	5.7	2.43 (0.41 to 16.77)	0.4198
N95[b]						
Direct contact with SARS patients	6	4.2	7	9.7	2.86 (0.70 to 13.71)	0.1683
Direct contact with patients in general[e]	5	3.6	3	4.2	1.28 (0.16 to 10.47)	1.0000
No patient contact[d]	14	10.2	12	17.1	1.83 (0.72 to 4.71)	0.2315
Goggles[b]						
Direct contact with SARS patients	12	8.4	23	31.9	6.41 (2.49 to 19.49)	<0.0001
Direct contact with patients in general[e]	7	5.1	16	22.2	6.93 (2.19 to 28.85)	0.0003
No patient contact[f]	19	13.9	21	30.0	3.50 (1.42 to 9.47)	0.0046
Gown[b]						
Direct contact with SARS patients	6	4.2	15	20.8	8.85 (2.46 to 48.28)	0.0002
Direct contact with patients in general[e]	2	1.4	12	16.7	11.54 (2.56 to 106.36)	0.0002
No patient contact[f]	16	11.7	19	27.1	3.42 (1.38 to 9.30)	0.0061
Gloves[b]						
Direct contact with SARS patients	2	1.4	11	15.3	20.54 (2.96 to 887.72)	0.0002
Direct contact with patients in general[e]	5	3.6	7	9.7	3.53 (0.77 to 21.85)	0.1211
No patient contact[f]	20	14.6	19	27.1	2.42 (1.05 to 5.81)	0.0374
Cap[b]						
Direct contact with SARS patients	8	5.6	17	23.6	7.30 (2.33 to 30.21)	0.0001
Direct contact with patients in general[e]	5	3.6	15	20.8	12.81 (2.92 to 116.75)	0.0001
No patient contact[f]	16	11.7	22	31.4	4.05 (1.68 to 10.76)	0.0009
No. of equipment inconsistently used with direct contact with SARS patients[g]						
0	129	90.2	45	62.5	1.00	
1–2	7	4.9	13	18.1	5.35 (1.79 to 18.53)	0.0015
≥3	7	4.9	14	19.4	7.84 (2.30 to 34.83)	0.0003
No. of equipment inconsistently used with direct contact with patients in general[e, g]						
0	127	92.0	52	72.2	1.00	
1–2	6	4.3	8	11.1	4.85 (1.01 to 31.86)	0.0479
≥3	5	3.6	12	16.7	10.83 (2.29 to 102.60)	0.0007
No. of equipment inconsistently used when there was no patient contact[d, g]						
0	113	82.5	46	65.7	1.00	
1–2	6	4.4	4	5.7	1.56 (0.28 to 7.97)	0.7721
≥3	18	13.1	20	28.6	3.40 (1.37 to 9.23)	0.0061

[a]SARS, severe acute respiratory syndrome; CI, confidence interval; OR, odds ratio.
[b]Those having no contact with patients were considered to be unexposed to the tabulated risk factor.
[c]Information on 4 controls missing.
[d]Information on 4 controls and 2 case-patients missing.
[e]Information on 5 controls missing.
[f]Information on 6 controls and 1 case-patients missing.
[g]Information on 6 controls and 2 case-patients missing.
[h]Including N95, goggles, gown, gloves and cap.

Table 2. Percentage with inconsistent hand hygiene[a]

Category	Controls (n = 143)		Case-patients (n = 72)		Matched OR (exact 95% CI)	p value (exact)
	n	%	n	%		
After direct contact with SARS patients	0	0	2	2.8	4.83 (0.38 to ∞)	0.2222
After direct contact with "patients in general"[b]	2	1.4	1	1.4	1.00 (0.02 to 19.21)	1.0000
When there was "no patient contact"[c]	3	2.1	10	14.3	6.38 (1.64 to 36.17)	0.0044

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Information on 3 controls missing.
[c]Information on 1 control and 2 case-patients missing.

wearing a N95 mask were wearing a surgical mask) were not statistically significant between cases and controls in any of the three settings (p > 0.05, Table 1).

When hospital workers were in direct contact with SARS patients, the case group was more likely to inconsistently use goggles (odds ratio [OR] = 6.41, p < 0.0001), gowns (OR = 8.85, p = 0.0002), gloves (OR = 20.54, p = 0.0002), and caps (OR = 7.30, p = 0.0001) than the control group. When in direct contact with patients in general, cases were more likely to inconsistently use goggle (OR = 6.93, p = 0.0003), gowns (OR = 11.54, p = 0.0002), and caps (OR = 12.81, p = 0.0001). When there was "no patient contact," cases had more than a twofold likelihood of inconsistently using goggles (p = 0.0046), gowns (p = 0.0061), gloves (p = 0.0374), or cap (p = 0.0009), compared to their matched controls. Having three or more personal protection equipment inconsistently used (including masks) was also a significant predictor of SARS infection for hospital workers in direct contact with SARS patients (OR = 7.84, p = 0.003); for those with direct contact with patients in general (OR = 10.83, p = 0.0007); and for those with no patient contact (OR = 3.4, p = 0.006) (Table1).

More than 97% of both the cases and control group consistently reported to practice good hand hygiene after contacting SARS patients or "patients in general" therefore differences between the two groups were not statistically significant (p = 0.22, and p = 1.00, respectively, Table 2). There was, however, a statistically significant difference in the proportion of cases (14.3%) and controls (2.1%) of hospital workers who reported inconsistent hand hygiene when there was "no patients contact" (OR = 6.38, 95% CI = 1.64, 36.2, p = 0.0044).

Perceived Inadequacy of Personal Protection Equipment Supply

A much higher percentage of SARS cases compared to controls reported a perceived inadequate supply of each of the 6 types of personal protection equipment (OR = 28.0, p < 0.0001 for surgical masks; OR = 5.19, p = 0.0004 for N95 masks; OR = 8.44, p < 0.0001 for gowns; OR = 29.3, p < 0.0001 for gloves; OR = 19.8, p < 0.0001 for goggles; OR = 52.4, p < 0.0001 for cap) (Table 3). Most notably, 44.4% of the cases reported that there was an inadequate supply of at least one item of the personal protection equipment, as compared to 14.0% of the controls (OR = 6.78, p < 0.0011); among SARS cases, 26% reported three or more personal protection equipment items as being in inadequate supply, compared to 1.4% of the controls (OR = 52.2, p < 0.0001).

SARS-Related Infection Control Training

The unadjusted results indicated that 50% of SARS cases did not receive any SARS infection control training (versus 28% of the controls) (Table 4). Those who underwent ≥2 hours of training (4.2% of cases and 25.2% of controls) were far less likely to have been infected with SARS (OR = 0.03, p < 0.0001). Of the SARS cases, 23.9% indicated that they did not understand the infection control

Table 3. Percentages with perceived inadequacy of personal protection equipment supply and breakthrough SARS infection among hospital workers[a]

Type of personal protection equipment	Controls (n = 143)		Case-patients (n = 72)		Matched OR (exact 95% CI)	p value (exact)
	n	%	n	%		
Surgical mask	1	0.7	14	19.4	28.00 (4.26 to ∞)	<0.0001
N95 mask	13	9.1	20	27.8	5.19 (1.95 to 16.13)	0.0004
Gown	7	4.9	19	26.4	8.44 (2.77 to 34.37)	<0.0001
Gloves	2	1.4	12	16.7	29.34 (4.79 to ∞)	<0.0001
Goggles	5	3.5	22	30.6	19.81 (4.83 to 174.55)	<0.0001
Cap	4	2.8	21	29.2	52.41 (9.08 to ∞)	<0.0001
Any one of above as inadequate[b]	20	14.0	32	44.4	6.78 (2.86 to 18.51)	<0.0001
No. of items identified to be inadequate[b]						
0	123	86.0	40	55.6	1.00	
1–2	18	12.6	13	18.1	3.25 (1.17 to 9.80)	0.0209
3	2	1.4	19	26.4	52.24 (7.70 to 2280.07)	<0.0001

[a]SARS, severe acute respiratory syndrome; OR, odds ratio; CI, confidence interval.
[b]Including N95 mask, goggle, gown, gloves and cap.

measures, compared with 8.5% of the controls (OR = 3.14, p = 0.0065). Duration of SARS training (<2 hrs versus ≥2 hours) was significantly associated with reported understanding of the infection control measures (OR = 7.29, p = 0.001). There was also a marginal statistically significant difference (OR = 0.27, p = 0.057) in the proportion who reported having received updated SARS information between case-patients (88.9%) and controls (96.5%).

Patient Care and Infection Control Measures

A higher but statistically nonsignificant percentage of the control group (73.4%) reported having direct contact with SARS patients as compared to the case group (62.5%). Three (4.2%) of 72 case-patients and 7 (4.9%) of 143 controls reported that they had no direct contact with patients in general (p > 0.05). Having performed high-risk procedures on SARS patients and being seconded from another unit were not significantly associated with risk of SARS infection (Table 4).

Table 4. Percentage distributions of variables related to training, patient care, social contact and mask compliance[a]

	Controls (n = 143)		Case-patients (n = 72)			
Characteristic	n	%	N	%	Matched OR (exact 95% CI)	p value (exact)
Length of SARS infection control training						
None	40	28.0	36	50.0	1.00	
<2hrs	67	46.9	33	45.8	0.47 (0.18 to 1.14)	0.1028
≥2hrs	36	25.2	3	4.2	0.03 (0.001 to 0.20)	<0.0001
Understood infection control measures[b]						
Yes	130	91.5	54	76.1	1.00	
No	12	8.5	17	23.9	3.14 (1.35 to 7.73)	0.0065
Acquired updated information						
No	5	3.5	8	11.1	1.00	
Yes	136	96.5	64	88.9	0.27 (0.06 to 1.04)	0.0574
High risk procedures with SARS patients[c]						
No	115	86.5	60	83.3	1.00	
Yes	18	13.5	12	16.7	1.22 (0.45 to 3.14)	0.8061
Direct contact with SARS patients						
No/Not sure	38	26.6	27	37.5	1.00	
Yes	105	73.4	45	62.5	0.57 (0.28 to 1.14)	0.1197
Direct contact with patients in general						
No/Not sure	7	4.9	3	4.2	1.68	1.000
Yes	136	95.1	69	95.8	(0.07 to 117.74)	
Seconded from another unit						
No	77	53.8	46	63.9	1.00	
Yes	66	46.2	26	36.1	0.60 (0.29 to 1.21)	0.1671
Social contact with SARS patients						
No/Not sure	95	66.4	55	76.4	1.00	
Yes	48	33.6	17	23.6	0.59 (0.28 to 1.19)	0.1592
Frequency of touching the N95[d]						
Never/occasional	108	76.6	46	70.8	1.00	
Most of the time/Always	33	23.4	19	29.2	1.32 (0.63 to 2.74)	0.5205
General problems with mask[e]						
No	72	51.4	41	59.4	1.00	
Yes	68	48.6	28	49.6	0.66 (0.34 to 1.27)	0.2407
Problems with mask fit[f]						
No	73	51.0	36	52.1	1.00	
Yes	70	49.0	33	47.8	1.00 (0.51 to 1.95)	1.0000
Problems with fogging of goggles[g]						
No	67	47.2	40	60.1	1.00	
Yes	75	52.8	26	39.9	0.61 (0.31 to 1.17)	0.1520
Overall problems in general compliance[h]						
No	69	50.0	41	58.6	1.00	
Yes	69	50.0	29	41.4	0.58 (0.25 to 1.33)	0.2264

[a]OR, odds ratio; CI, confidence interval; SARS, severe acute respiratory syndrome.
[b]Information on 1 control and 1 case-patient missing.
[c]Information on 10 controls with direct contact with SARS patients missing.
[d]Excluded 2 controls and 6 case-patients who did not use N95 mask; information on 1 case-patient missing.
[e]Excluded 1 case who did not use mask; information on 3 controls and 2 case-patients missing.
[f]Excluded 1 case who did not use mask; information on 2 case-patients missing.
[g]Excluded 3 cases who did not use goggle; information on 1 control and 3 case-patients missing.
[h]Excluded 1 case who did not use any equipment; information on 5 controls and 1 case-patient missing.

There were no significant differences between the percentages of case-patients and controls who reported the following problems: general compliance problems, frequency of touching or adjusting the N95 mask, general problems with mask, problems with mask fit, and problems with fogging of goggles (Table 4).

Social Contact with SARS Cases

Approximately 23.6% of the SARS case-patients and 33.6% of the matched controls reported ever having social contact with someone who was later diagnosed with SARS before the onset of symptoms of the relevant case-patients ($p = 0.1592$) (Table 4).

Problems Encountered

Seven problems in the unadjusted analysis (Table 5) were significantly associated with risk for SARS infection. An indicator variable was constructed by counting the number of problems encountered by the study participants. Almost all (98.6%) of the case group encountered at least one problem (versus 79.9% in the control group). The risk increases greatly with the number of problems encountered (OR = 44.2 for 3 or more problems, $p < 0.0001$) (Table 5). Using a cut-off point of two or more problems to predict SARS infection gives a sensitivity and specificity of 0.681 and 0.691, respectively.

Multivariate Analysis

The results of the forward stepwise conditional logistic regression model using the seven significant variables as candidate variables indicate that the perceived inadequacy of personal protection equipment supply (adjusted OR = 4.27, 95% CI 1.66 to 12.54, $p = 0.0028$), SARS infection control training <2 hours or no training (adjusted OR = 13.6, 95% CI 1.24 to 27.50, $p = 0.002$), and inconsistent use of more than one type of personal protection equipment when having direct contact with SARS patients (adjusted OR = 5.06, 95% CI 1.91 to 598.92, $p = 0.02$) were significantly and independently associated with SARS infection among hospital workers.

Discussion

Breakthrough transmission was likely responsible for the SARS infection of these cases, as protective masks (primarily N95) were used consistently by almost all of the cases. All workers were required to wear protective masks from March 12, 2003. Using protective masks alone is, therefore, not sufficient to eliminate SARS transmission among hospital workers. Cases were less likely to have had direct contact with a SARS patient than controls, suggesting that direct physical contact with SARS patients was not necessary for breakthrough transmission to occur. It also suggests that modes of transmission other than droplets cannot be excluded. Consistent hand hygiene after contact with patients was almost universal and was not a significant factor predicting SARS transmission in our study, although hand hygiene appeared to be a risk factor in situations when there was no patient contact.

Data from all the three settings show that inconsistent use of gown, cap, and goggles were all very strongly associated with breakthrough transmissions. Personal protection equipment should be used consistently in all three settings. The high degree of collinearity in the use of the various types of personal protection equipment makes it difficult to ascertain which type of personal protection equipment is most important as a SARS countermeasure. Nevertheless, policy makers should be made aware that the supply of different types of personal protection equipment had often been seen as inadequate, and it is one of the very significant risk factors identified. The perception of inadequate supply was not verified by this study. These perceptions may reflect the actual situation or may be an inaccurate impression of the hospital workers. Caution is advised in interpreting these results. Nevertheless, at the time of the study, the media had reported frequent complaints about personal protection equipment supply shortages from hospital workers. The perception of inadequate personal protection equipment is likely to be associated with the personal protection equipment supply situation. Given the large differences in our results (OR > 5.0, $p < 0.001$), it is likely that personal protection equipment

Table 5: Percentage distribution of the number of problems encountered by the hospital worker[a]

No. of problems encountered[b]	Controls			Case-patients			Matched OR (exact 95% CI)	p value (exact)
	n	%	Cumulative %	n	%	Cumulative %		
0	27	20.1	20.1	1	1.4	1.4	1.00	
1	65	48.5	68.6	21	30.4	31.8	8.47(1.37 to ∞)	0.0169
2	24	17.9	86.5	17	24.6	56.4	17.78(2.67 to ∞)	0.0010
≥3[c,d]	18	13.4	100.0	30	43.5	100.0	44.15(7.02 to ∞)	<0.0001

[a]Excluded nine controls and thee cases that had at least one missing entry on one of the problems encountered.
[b]The seven problems are: 1) inconsistent use of at least 1 type of personal protection equipment when having contact with SARS patients, 2) with "patients in general," 3) when there was "no patient contact," 4) when SARS infection control training was less than 2 hours, 5) when the respondent reported not understanding SARS infection control procedures, 6) when at least one personal protection equipment was perceived to be in inadequate supply in the 3 settings, and 7) when hand hygiene was inconsistent when there was "no patient contact."
[c]Percentages of the number of problems encountered in the control group: 3 problems (6.7%), 4 problems (4.5%), 5 (1.5%), 6 (0.7%), and 7 (0%).
[d]Percentages of the number of problems encountered in the case group: 3 problems (10.1%), 4 (8.7%), 5 (13.0%), 6 (8.7%), and 7 (2.9%).

shortages were at least partially responsible for many of the SARS infections. As inadequate knowledge of SARS infection control ("did not understand procedures") is also a strong risk factor for breakthrough transmission, SARS infection control training must not be overlooked. In-depth, thorough training (≥2 hrs) is required.

Soon after the initial SARS outbreak, it was mandatory for all hospital workers to attend at least one 1-hour structured training session delivered by the infection control team, and the records of these sessions were collected and submitted to the Hospital Authority. These training sessions were conducted twice per day for the initial week from the middle of March and daily until the end of June. The content of these training sessions included basic knowledge of SARS and its clinical presentation, route of transmission, types and proper use of different personal protective equipment for different risk levels, the procedures for handling high risk specimens, environmental disinfection protocols, and commonly observed problems. The content of the training was regularly revised with updated information. Regular updates and attendance of the training sessions were strongly recommended. The unit supervisors were given more intensive training to train their staff. The findings of this study underscore the importance of in-depth training in SARS prevention among hospital workers.

The findings eliminate a number of speculated risk factors which include the following: performing particular high-risk procedures on SARS patients, having social contacts with people who were later found to have SARS cases, and experiencing various minor problems in using the mask. Performing high-risk procedures was not a significant factor, hence, it is speculated that this is due to a high degree of awareness and caution taken when performing these procedures with SARS patients.

It is found that those who encountered any of the seven identified problems had a greatly increased likelihood of contracting SARS. The number of problems encountered is a strong predictor of SARS infection. It is recommended that, after each day's work, health workers complete a checklist to be reviewed by management. No hospital staff should be exposed to SARS before receiving adequate training or before they have obtained a thorough understanding of the infection control procedures. The results of the multivariate analysis show that infection control training, personal protection equipment use, and perceived supply were independently associated with SARS infection risk among hospital workers.

This study has a number of limitations. As a case-control study, it is subject to recall bias. However, the recall period was usually within 1 week as all the case-patients were interviewed while they were hospitalized. Hand hygiene data were self-reported and not audited. Nevertheless, since respondents were required to report the frequency of hand washing from a categorical response format rather than an open ended question, the responses should be reasonably reliable. Another possible bias may be the case group's attributing their infection to external factors (e.g., inadequate supplies) and the control group's doing the opposite. Given that the odds ratios obtained were strongly significant and consistent with one another, it is unlikely that this form of bias could account for all of the observed differences. The study, however, has a relatively large sample size, a high response rate, and has controlled for the exposure to other background confounding factors.

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Dr. Lau is the director of the Centre for Epidemiology and Biostatistics of the School of Public Health of the Chinese University of Hong Kong. One of his research interests is the behavorial aspects of infectious diseases.

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Address for correspondence: Joseph T.F. Lau, Centre for Epidemiology and Biostatistics, Faculty of Medicine, The Chinese University of Hong Kong, 5/F, School of Public Health, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR; fax: (852) 2645-3098; email: jlau@cuhk.edu.hk

Cluster of SARS among Medical Students Exposed to Single Patient, Hong Kong

Tze-wai Wong,* Chin-kei Lee,† Wilson Tam,* Joseph Tak-fai Lau,* Tak-sun Yu,* Siu-fai Lui,‡ Paul K.S. Chan,* Yuguo Li,§ Joseph S. Bresee,¶ Joseph J.Y. Sung,* and Umesh D. Parashar,¶ for the Outbreak Study Group*[1]

We studied transmission patterns of severe acute respiratory syndrome (SARS) among medical students exposed exclusively to the first SARS patient in the Prince of Wales Hospital in Hong Kong, before his illness was recognized. We conducted a retrospective cohort study of 66 medical students who visited the index patient's ward, including 16 students with SARS and 50 healthy students. The risk of contracting SARS was sevenfold greater among students who definitely visited the index case's cubicle than in those who did not (10/27 [41%] versus 1/20 [5%], relative risk 7.4; 95% confidence interval 1.0 to 53.3). Illness rates increased directly with proximity of exposure to the index case. However, four of eight students who were in the same cubicle, but were not within 1 m of the index case-patient, contracted SARS. Proximity to the index case-patient was associated with transmission, which is consistent with droplet spread. Transmission through fomites or small aerosols cannot be ruled out.

Severe acute respiratory syndrome (SARS) is a newly recognized clinical entity associated with infection by a novel coronavirus (SARS-CoV) (1–4). SARS is characterized by symptoms of fever, chills, headache, and dry cough, with radiographic evidence of pneumonia in most patients. The incubation period of SARS is estimated to be a median of 4 to 6 days (range 2–10 days). SARS is contagious, and person-to-person transmission appears to occur primarily through contact or respiratory droplets (5). However, because of the efficient transmission of SARS observed in some situations (6,7), concerns remain about the spread of SARS-CoV through other means, including small aerosols or contact with contaminated environmental surfaces.

The pandemic of SARS is believed to have originated in late 2002 in Guangdong Province, China (5). A SARS patient from this region, who had onset of illness on February 15, 2003, traveled to Hong Kong and may have infected several guests at the hotel where he resided during February 21–22. One of the affected hotel guests was a resident of Hong Kong; on February 24, he exhibited an illness characterized by fever, cough, runny nose, and malaise. His symptoms worsened over the next few days, leading to his hospitalization on March 4 at the Prince of Wales Hospital, a major teaching hospital of the Chinese University of Hong Kong. The cause of this patient's illness was not recognized until March 10, when secondary cases of SARS were first reported among healthcare workers; specific infection control measures were then implemented.

Epidemiologic investigations indicate that this patient transmitted SARS to 47 healthcare workers on the ward to which he was admitted; the administration of a bronchodilator through a jet nebulizer was widely believed to have contributed to this dramatic pattern (1). SARS developed in all but one of the 16 nursing staff members on the ward and in all 6 ward physicians. The first patient with a secondary case of SARS, which presumably resulted from infection by this index patient, was not hospitalized until March 11. Therefore, the period from March 4 to 10 provided a risk window during which the factors that affected transmission of SARS among persons exposed exclusively to this index patient could be assessed.

*The Chinese University of Hong Kong, Hong Kong Special Administrative Region (SAR), People's Republic of China; †National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australia; ‡Hospital Authority, Hong Kong SAR, People's Republic of China; §The University of Hong Kong, Hong Kong SAR, People's Republic of China; and ¶Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[1]Members of the outbreak study group: Nelson Lee and Jean Kim, The Chinese University of Hong Kong; Kitty Fung and Albert Ng, Prince of Wales Hospital, Hong Kong; Kazutoshi Nakashima, Tomi Sunagawa, Keiji Fukuda, Tracee Treadwell, and Udo Bucholz, World Health Organization, Geneva, Switzerland; M.K. Tham and Thomas Tsang, Hong Kong Department of Health, Hong Kong.

Although several groups of healthcare workers were exposed to SARS, some groups (e.g., ward nurses and doctors) could not provide useful information because most were affected by SARS, and other groups (e.g., staff in the accident and emergency department) could not recall all of their exposures to the index patient. However, a group of medical students who visited the ward had limited, well-defined exposures that could be accurately recalled. These included 20 third-year medical students who performed a bedside clinical assessment in the ward on the mornings of March 6 and 7, supervised by a team of assessors from the university. Each student was assigned to examine specific patients in the ward during a 40-minute interval on 1 of the 2 days. The locations (bed numbers) of the patients assigned to each student were precisely known, as well as the relative location of these patients to the index SARS case-patient. In addition to the students who appeared for the assessments, several other students (mostly fifth-year students) visited the ward for bedside teaching or clinical training March 4–10. We analyzed the epidemiologic features and patterns of transmission of SARS among these students.

Methods

Study Population

We conducted a retrospective cohort study of medical students who visited the index patient's ward from March 4 to March 10, 2003. To define the study cohort, all 474 medical students of the university who were in their clinical years (years 3–5) were contacted to inquire whether they had visited the patient's ward during this period. Because the university classes were suspended in response to the outbreak at the time this investigation was begun, the students were contacted by electronic mail.

Data Collection

Students who reported visiting the patient's ward during the period were given a detailed questionnaire that sought information about demographic characteristics, history of recent illnesses, activities in the ward (including specific exposure to the index patient), use of personal protective equipment, and history of travel March 1–10. Students who contracted SARS were interviewed in the hospital wards where they were admitted. To facilitate the recall of exposures to the index patient, a map showing the location of the index patient on the ward was distributed with the survey. Survey responses were validated by a follow-up telephone interview or electronic mail communication. Data provided by students regarding the bed numbers of patients they examined during their bedside clinical assessment were cross-checked with the university records. The medical (including nursing) records of the index patient and the students who were ill with SARS were reviewed.

Case Definition

A case of SARS was defined by the presence of fever (temperature >38°C) and evidence of pneumonia on either a radiograph or computed tomographic image of the thorax, with or without respiratory symptoms (e.g., cough and shortness of breath).

Laboratory Studies

Paired serum specimens were obtained during the acute phase and convalescent phase (day 21 from onset of fever) of illness from ill students, and single serum samples were obtained during April 26 to May 3 from students who visited the ward during March 4 to 10 but did not acquire SARS. The serum specimens were tested for anti–SARS-CoV immunoglobulin (Ig) G by indirect immunofluorescence, by using SARS-CoV–infected Vero cells fixed in acetone. A positive test was defined as either seroconversion (≥4-fold rise in antibody titer in the paired serum specimens) or a convalescent-phase antibody titer of >1:40.

Ventilation Study

Information on the ward ventilation system was first obtained from the Electrical and Mechanical Services Department of the hospital. A detailed assessment of the ventilation system and airflow studies could not be performed at the time of the outbreak because of logistic constraints. Retrospective on-site inspections and measurements of the ventilation design and air distribution were carried out on July 17 and July 22. The supply and exhaust airflow rates were measured by a hood flow rate meter (APM 150) (TSI Inc., Shoreview, MN) (measurement range 24–945 L/s with an accuracy of 3%). Air velocity, air temperature, and relative humidity at all supply diffusers and exhaust grilles were measured by a portable VELOCICALC Plus air velocity meter Model 8386A (TSI Inc.). Information on the location and opening sizes of supply diffusers and exhaust grilles, as well as information on the distribution of heat sources such as lighting and the number of persons in the ward, were also collected during the site visits.

Data Analysis

Epidemiologic data were entered into a predesigned database and analyzed by using SAS Version 6.12 software (SAS Institute Inc., Cary, NC). Attack rates among persons with and without specific exposures were calculated. Dose-response relationships were also evaluated with respect to the proximity to the index patient and duration of these exposures.

Data on ventilation, temperature, relative humidity, and heat sources were analyzed by computational fluid dynamics (CFD) simulations. The industry standard CFD package, Fluent, (Fluent USA, Lebanon, NH) was used to predict (reproduce) the average airflow pattern in the ward during the outbreak, taking into consideration the effect of thermal buoyancy.

Results

Clinical Course of the Index Patient's Illness

On February 24, the index case-patient had onset of an illness characterized by fever, cough, runny nose, and malaise. His symptoms worsened over the next few days, and he sought treatment at the Accident and Emergency Department of the Prince of Wales Hospital on February 27, when he was treated as an outpatient and discharged. He visited the Accident and Emergency Department again on March 4 with the same symptoms and was admitted to a general medical ward. His fever (range 38°C–40°C) did not diminish after he received various antimicrobial drugs and persisted until March 11, when it gradually subsided. His cough was frequent, low-pitched, and unproductive, with occasional scanty, whitish sputum, and it persisted from March 4 to March 13; the cough was most severe during the first 4 days of his hospitalization, March 4–7. His chest radiograph on admission showed consolidation of the right upper lobe and patchy haziness in the right lower zone. He was weak, was given an intravenous drip, and remained bedridden during his first week of hospitalization. To relieve his respiratory symptoms, he was administered salbutamol through a jet nebulizer four times per day (at 10 a.m., 2 p.m., 6 p.m., and 10 p.m.) starting from 2 p.m. on March 6 until March 12, lasting about 30 min each time. His arterial oxygen on admission was 99%; it dropped to 95% on March 6, and gradually returned to 98% on March 12. He was identified as the index patient for the outbreak of SARS in Prince of Wales Hospital on March 12 and was transferred to an isolation room within the ward. He remained in isolation for 17 days after his symptoms subsided and was discharged on March 30. The patient was not treated with either ribavirin or steroids.

Medical Student Study

Of the 474 medical students, 334 (70.5%) responded to the survey. Of the 334 respondents, 66 (20%) reported visiting the index patient's ward during the study period. Respondents and nonrespondents did not differ in age and gender. SARS did not develop in any of the nonrespondents or in any of the respondents who did not visit the index patient's ward. A detailed survey to assess illness and exposures was completed by these 66 students, which included the group of 20 third-year medical students who performed a bedside clinical assessment, supervised by a team of assessors from the university, in the ward on March 6 and 7, and 46 other students who visited the ward for clinical training on one or more occasions from March 4 to 10. None of the 20 students who appeared for the bedside clinical assessment visited this ward after March 7 or had any contact with other SARS patients in this hospital or in the community.

Sixteen (24%) of the 66 students reported an illness that met the case definition for SARS. Their mean age was 22.3 years, and 8 (50%) were male. The mean age of the 50 other students who visited the ward but did not acquire SARS was 23.2 years, and 23 (46%) were male. The most common symptoms of illness among the patients included fever (100%), chills or rigors (94%), and headache (75%); cough and shortness of breath were reported by 38% and 33% of patients, respectively (Figure 1). All ill students were hospitalized, and one required mechanical ventilation and treatment in the intensive care unit; all recovered from the illness. The characteristics of the illness among the students were similar to those among healthcare workers presumably infected by the index patient.

Paired serum specimens were collected from 15 of the 16 students during their illnesses, and all had demonstrable IgG antibodies to SARS-CoV at a titer of >1:40 in the convalescent-phase serum. The antibody titer ranged from 1:80 to 1:1,280, with a geometric mean titer of 1:440. Antibodies to SARS-CoV were absent in the serum specimens obtained from all 50 healthy students.

The dates of onset of illness of the 16 students with SARS and the dates they visited the ward are shown in Figure 2. The student with an unusually long incubation period of 16 days visited the ward (for a 40-minute bedside clinical assessment) on March 7. On March 13, she was noted to have pneumonic changes on a chest radiograph, although she had no symptoms. She was admitted to an observation ward for suspected SARS patients (different from the index patient's ward) and was discharged on March 17 after resolution of her chest radiographic abnormalities. On March 23, fever developed, and she was

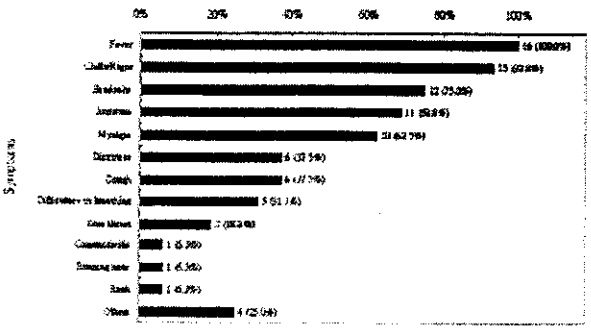

Figure 1. Distribution of initial symptoms in 16 students.

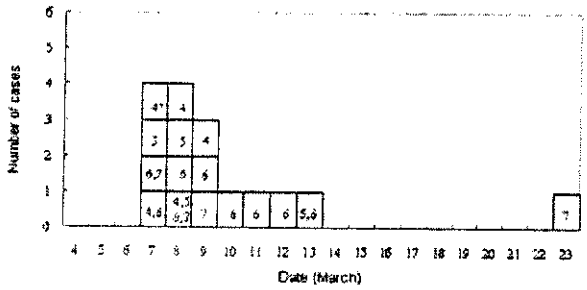

Figure 2. Dates of onset of illness of 16 students with severe acute respiratory syndrome and date of their visit to the index patient's hospital ward. An asterisk indicates the dates of the visit in March 2003.

readmitted as a potential SARS case-patient. Because we were not certain if this student had been infected during her initial exposure to the index case or during her subsequent hospitalization by exposure to another SARS patient in the observation ward, we excluded this student from the analyses of risk exposures. To obtain a precise estimate of the incubation period of SARS, we examined the onset of illness among 11 of the 16 ill students who visited the ward only on a single day, excluding the student with an incubation of 16 days. Among these 11 patients, the median incubation period was 3 days (range 2–6 days). Figure 3 shows the incubation period by onset date. Students exposed on March 6 had the widest range of incubation period (2–6 days). Too few students were exposed exclusively on other days to show any pattern.

We examined the attack rates of the illness among students based on whether they could recall entering the index patient's cubicle, a semi-enclosed section of the ward containing 10 beds (Table 1). SARS developed in 10 of the 27 students who reported entering this cubicle, compared with SARS developing in 4 of the 18 students who could not accurately recall whether they entered the patient's cubicle, and in only 1 of 20 students who reported that they never entered the cubicle (Mantel-Haenszel chi-square = 6.54; p = 0.011; Fisher exact test [2-tailed], p = 0.032). The student who did not enter the index patient's cubicle but acquired SARS was a fifth-year student (not one of the third-year students who underwent the bedside clinical assessment) who reported visiting the patient in bed no. 17x, which was located in the opposite cubicle adjacent to the corridor (Figure 4). Among those students who could recall accurately whether they entered the patient's cubicle, entering the cubicle was significantly associated with illness (10/27 versus 1/20, relative risk = 7.4, 95% confidence interval = 1.0 to 53.3, p = 0.046). The duration the students stayed in the ward was not associated with the risk for illness (mean length of stay: 67 minutes for the ill students; 80 minutes for the healthy students; p = 0.6).

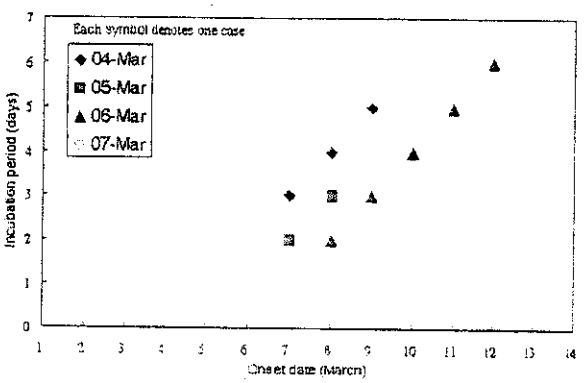

Figure 3. Incubation period by onset dates in 11 students.

Table 1. Attack rate of students by history of visit to index patient's cubicle in the ward

Entered index patient's cubicle	Ill	Not ill	Total	Attack rate (%)[a]
Yes	10	17	27	37.0
Not sure	4	14	18	22.2
No	1	19	20	5.0
Total	15	50	65	23.1

[a]Fisher exact test (2-tailed), p = 0.032; Mantel-Haenszel chi-square = 6.54; p = 0.011.

To further assess the proximity of exposure associated with illness, we analyzed data from 19 of 20 medical students (excluding the ill student who had an unusually long incubation period) who appeared for the bedside clinical assessment (lasting 40 minutes for each student) on March 6 or 7. SARS developed in 7 of these 19 students. None of the students examined the index patient. All three students who examined patients located in beds within 1 m of the index patient contracted SARS; four of eight students who examined patients located in the same cubicle but in beds >1 m from the index patient contracted SARS, but none of eight student who examined patients in other cubicles fell ill (Mantel-Haenszel chi-square = 9.86, p = 0.002; Fisher exact test [2-tailed], p = 0.0031) (Table 2; Figure 4).

As mentioned previously, the index patient was administered nebulizer therapy four times per day starting from 2 p.m. on March 6 until March 12, lasting about 30 minutes each time. Among all the students, no significant association was noted between their risk for illness and presence in the ward when the nebulizer was in use. To further study the potential role of nebulizer therapy in disease transmission, we studied the temporal patterns of illness among these 19 students who appeared for a bedside clinical assessment, excluding the student with a long incubation period (Table 3). Six out of 10 students assessed on March 6 before the nebulizer was used contracted SARS compared with 1 out of 9 students on March 7. The time of assessment of the student with SARS (on March 7) coincided with the use of the nebulizer.

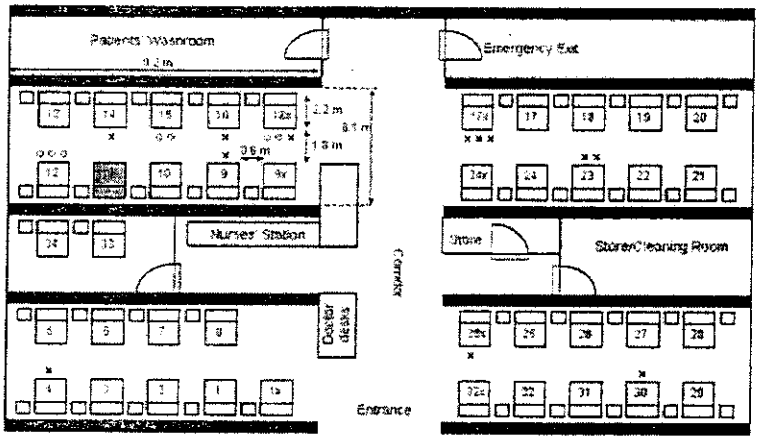

Figure 4. Floor plan of index patient's hospital ward. Numbers with and without a suffix indicate the bed numbers of patients. The bed of the index patient is shaded. 0, students assigned to examine the patient in this bed who became ill with severe acute respiratory syndrome; x, students assigned to examine the patient in this bed who remained healthy.

The medical students were assessed by a total of 11 assessors. Five assessors evaluated students on March 6 only, five on March 7 only, and one was present on both days. SARS was reported by all five assessors for March 6 only, by three of five assessors for March 7 only, and by the one assessor who was present on both days.

None of the students had traveled to mainland China, the only location with suspected community transmission of SARS during the study period. None of the ill students reported contact with another ill student or other person with SARS in the 10 days before illness onset. None wore masks or gloves while examining patients, and no notable differences in risk for disease were observed among students who reported washing their hands before and after examining patients. Apart from one hepatitis B carrier (who contracted SARS), no other students had any chronic illness. The clinical course and severity of illness in the hepatitis B carrier were similar to the experiences of other students.

Table 2. Attack rate for students attending a bedside clinical assessment in the ward in relation to their proximity to the index patient's bed[a,b]

Location of exposure	Cases/no. of students exposed
Bed nos. 10 and 12 (adjacent to index patient)	3/3
Bed nos. 9, 9x, and 13–16x (beds in the same cubicle except bed nos. 10–12)	4/8
Other beds in the ward (not in the cubicle)	0/8

[a]The index patient was not used as an assessment case.
[b]Mantel Haenszel chi-square = 9.86, p=0.002; Fisher exact test (2-tailed), p = 0.0031.

Ventilation Study

Ventilation System

The hospital is centrally air-conditioned. Fresh air is drawn from outside the hospital building into a primary air unit situated in a room adjacent to the ward, where it is cooled by chilled water and then supplied to this ward (and another ward on the opposite side of the hospital) through air ducts. The air is then distributed to five fan-coil units (one in each of the four cubicles and one at the nurses' station), where it is mixed with recirculated air, cooled by chilled water, and blown into the cubicle/nurses' station via air supply diffusers (0.6 m by 0.6 m) located at the center of the cubicle in the false ceiling and over the nurses' station. An exhaust grille, a rectangular opening 0.3 m by 0.6 m, located in the false ceiling in the corridor outside each cubicle and outside the nurses' station, recirculates 70% of the air supply back into the fan-coil unit. Excess air escapes through two extraction fans inside the toilet, two extraction fans in the store/cleaning room, and through the door of the ward to the outside.

Airflow Measurements

The air exchange was 7.79 air changes per hour for the whole ward. The supply and exhaust airflow rates are summarized in Figure 5. The total air supply was higher than the total exhaust, which meant that the ward was at a positive pressure. Our on-site measurement showed that most of the extra air supply should have exited through the ward entrance because an exhaust fan was located in both the

Table 3. Time schedule of the clinical assessment of 19 medical students[a]

Time		Ill/total
6 March 2003	10:00–10:40 a.m.	0/3
	10:40–11:20 a.m.	2/3
	11:30 a.m.–12:00 p.m.	3/3
	12:00–12:40 p.m.	1/1
7 March 2003	10:00–10:40 a.m.	1/2
	10:40–11:20 a.m.	0/3
	11:30 a.m.–12:00 p.m.	0/3
	12:00–12:40 p.m.	0/1

[a]Excluding the student-patient whose illness had a long incubation period.

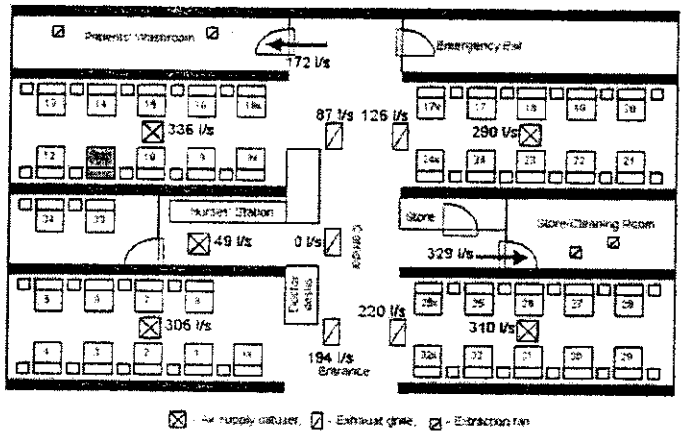

Figure 5. Airflow rates (L/s) through all air supply diffusers and exhaust grilles in the index patient's hospital ward.

primary air unit room and the kitchen, just outside the entrance to the ward; these fans would create negative pressure.

The supply and exhaust airflow rates through diffusers and exhaust grilles were found to be imbalanced. The exhaust and air supply for the nursing station did not function properly. The air supply from the diffuser in the index patient's cubicle had the highest supply flow rate (336 L/s), while the adjacent exhaust grille had the lowest exhaust flow rate (87 L/s) among all four functional exhaust grilles.

Modeling the Dispersion of Hypothetical Aerosols

At the time of the outbreak (March 4–10), the weather in Hong Kong was moderate with an ambient temperature ranging from 10.5°C to 22.3°C. The heat gains in the ward should be mainly from people, lighting, and equipment. In our computational fluid dynamics simulations to reproduce the average airflow pattern in the ward during the outbreak, we excluded the washroom and storeroom in our computational domain; and the exhaust flows through the two rooms were modeled as exhaust flows through their doorways. A free boundary condition was imposed on the ward entrance. Our computational fluid dynamics package could also consider the movement and evaporation of the aerosols. We found that aerosols would rapidly evaporate and the size of droplets would decrease rapidly after they originated from the index patient's bed. The average air speed in the room was around 0.2 m/s. The normalized concentration contours of hypothetical aerosols are shown in Figure 6. The concentrations decreased as we moved away from the index patient's bed. We also predicted a fairly high concentration profiles for beds 17x and 24x in the opposite cubicle. The concentrations in other two cubicles were almost zero.

Discussion

We utilized a unique opportunity provided by an unrecognized SARS patient who was the only known source of infection for a large cluster of secondary cases in an institutional setting to examine the transmission patterns of this novel disease. Proximity to the index case was associated with transmission, and all three students who examined the patient in bed 12 (within 1 m of the index patient) contracted SARS. As the index patient was bedridden during this period, this observation is compatible with transmission by droplets. However, that a few ill students were never within 1 m of the index patient raises the possibility of transmission by other mechanisms. Spread by contaminated fomites is a possibility, especially in light of recent data indicating that SARS-CoV survives well in the environment (8). Although none of the students reported direct contact with any of the index patient's belongings or linen, contact with other articles in the ward contaminated by the

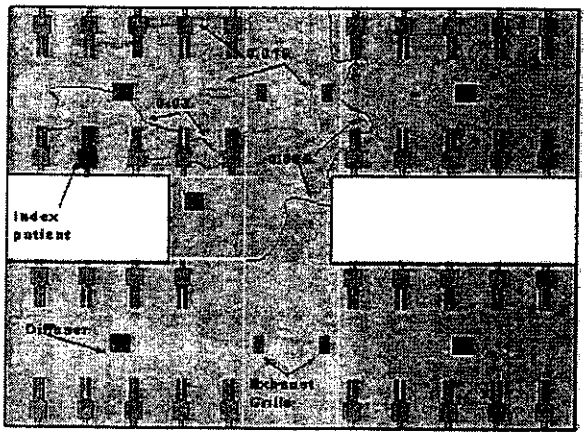

Figure 6. Dispersion of hypothetical aerosols that originated from the index patient's bed in the ward. Three levels of normalized concentrations are shown (0.03, 0.015, and 0.005) because the source strength of the virus-laden aerosols is unknown.

patient's secretions or body fluids might have occurred. Transmission by aerosols over a limited distance could also explain the observed distribution of cases and the large number of cases among healthcare workers on the ward. In our ventilation study, we found that the airflow rate was highest in the air supply diffuser in the index patient's cubicle and lowest in the corresponding exhaust grille. This imbalance and the computed concentration contours of aerosols (which match our epidemiologic data) are compatible with spread by aerosols. However, because we were not able to conduct a detailed study of ventilation patterns or conduct environmental and air sampling at the height of the outbreak due to logistic constraints, we cannot definitively assess whether either fomites or aerosols played a role in transmitting virus from the index patient.

At the time this investigation was begun, jet nebulizer therapy given to the index patient was widely believed to have facilitated transmission. However, our findings demonstrate efficient transmission even before nebulizer therapy was begun on the afternoon of March 6. First, 6 of the 10 students who attended the bedside clinical assessment on the morning of March 6 contracted SARS, compared with 1 of the 9 who attended the assessment on March 7. Second, all five of the assessors who assessed students on March 6 alone became ill, compared with three of the five assessors who were present on March 7 alone. Lastly, for the students with SARS who were present on the ward for reasons other than the bedside assessment, no association was observed between their stay in the ward at the specific periods when the nebulizer was used and the development of SARS. However, because nebulizer therapy could theoretically exacerbate symptoms of coughing in SARS patients, we recommend avoiding the use of nebulized medications and other potential aerosol-generating patient-care procedures if possible and using appropriate infection control precautions if such procedures are deemed necessary (9).

Similar large "superspreading events" of SARS associated with a single patient have been described in several countries (5,6), which contrast with the limited secondary spread seen with most SARS patients. Because many of the index patients in these clusters were infected with early cases of SARS in their respective countries, such as the index patient for this outbreak, or had subtle or atypical manifestations, the failure to recognize the disease early and institute appropriate infection control precautions might have contributed to extensive transmission. Also, some SARS patients may be intrinsically more contagious. They might excrete greater amounts of virus in their secretions or transmit virus by different routes, which may be related to specific host (e.g., altered immune status, underlying diseases), agent (e.g., coinfections with other pathogens), or environmental factors that require further study. Superspreading events have been reported in outbreaks of other diseases such as Ebola hemorrhagic fever, rubella, and β-hemolytic streptococci (10–12). While the mechanisms for these phenomena are largely unknown, possible explanations include a larger number of contacts of these superspreaders, inherent differences in the virus-host relationship, or the presence of a more virulent strain or higher levels of virus shedding (10). Similarly, hospitals have previously been documented as settings for efficient transmission of illnesses such as Lassa fever and Bolivian hemorrhagic fever (13,14).

In conclusion, this cluster demonstrates the potential for widespread nosocomial spread of SARS among a previously healthy population in the absence of specific infection control precautions. SARS is likely spread through direct contact and respiratory droplets in most instances, and others have demonstrated that specific infection control precautions to prevent transmission by these mechanisms are effective (15). However, we cannot exclude the role of contaminated fomites or small aerosols in transmitting virus in this outbreak. Whether this large cluster resulted from different mechanisms of transmission, greater viral shedding by the patient, or inadequate infection-control measures is not known, but it clearly indicates that SARS can be spread highly efficiently in some situations. A better understanding of the phenomenon of superspreading events, including clusters with apparently unique patterns (15), is key to assessing the pandemic potential of SARS and the effectiveness of control measures (16,17).

Acknowledgments

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Prof. Wong currently teaches epidemiology and public health in the Department of Community and Family Medicine, the Chinese University of Hong Kong. His research interests include viral infections (hantaviruses and SARS) and environmental health.

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Address for correspondence: Tze-wai Wong, Department of Community and Family Medicine, The Chinese University of Hong Kong, 4/F, School of Public Health, Prince of Wales Hospital, Shatin, NT, Hong Kong SAR, People's Republic of China; fax: (852) 26063500; email: twwong@cuhk.edu.hk