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Prevalence of Subclinical Infection by the SARS Coronavirus among General Practitioners in Hong Kong

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Eight general practitioners had severe acute respiratory distress syndrome (SARS) in Hong Kong during the epidemic, and others may have been infected by the SARS coronavirus without developing the full syndrome. We conducted a serological and questionnaire survey to determine the prevalence of subclinical infection by SARS coronavirus among general practitioners in Hong Kong. Participants had to be doctors actively practising in family medicine and who did not have SARS. Approximately 3200 general practitioners were invited to participate and the results of 574 were eligible for analysis. 29 samples were tested positive by enzyme-linked immunosorbent assay, but all these samples had titre <25 by immunoflorescence assay. The prevalence for seropositivity was thus 0% (95% CI, 0.0%–0.6%). This finding documents the lack of subclinical infection by SARS coronavirus in an at-risk group in the community.

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INTRODUCTION

Severe acute respiratory syndrome (SARS) originated in Guangdong Province in China in mid-November 2002, and went on to cause a major epidemic in Guangzhou and other nearby cities in January and February 2003 (1). The Hong Kong Special Administrative Region (HKSAR) is geographically close to the epicentre and traffic between HKSAR and these cities is high, and sporadic cases of SARS began to appear in Hong Kong as early as January 2003 (unpublished data from T. Tsang). The arrival of an infected doctor in a Hong Kong hotel on 21 February 2003 triggered an epidemic in Hong Kong as well as in Canada, Singapore, Vietnam, and elsewhere (2).

The clinical and radiological features of SARS have been well described (3–5). Before its aetiology became known, the World Health Organization (WHO) defined probable SARS as satisfying all of the following criteria: (i) fever of 38°C or higher, (ii) new infiltrates in the chest radiograph, (iii) either cough or shortness of breath, (iv) visited or resided in a SARS-affected area within 2 months, and (v) no other cause that can entirely explain the illness. With the discovery of a novel coronavirus as the causative agent of SARS, laboratory tests were developed that greatly aided diagnosis. The use of reverse transcriptase-polymerase chain reaction (RT-PCR) to detect viral RNA, the detection of antibodies to the SARS-coronavirus (SARS-CoV) by enzyme-linked immunosorbent assay (ELISA) or immunoflorescence assay (IFA), and virus isolation were subsequently incorporated into the WHO surveillance definition of probable SARS (6).

There were 1755 cases of probable SARS in Hong Kong. At the onset of their illness, the majority of them presented to their general practitioners (GPs) before being admitted to hospital at around d 4 of illness. GPs were therefore at increased risk of exposure to SARS-CoV. While 8 GPs did have SARS, the majority did not, and it was possible that some may have been infected by SARS-CoV but either did not develop the full syndrome or were asymptomatic. Transient subclinical infection among respiratory viruses is common and well documented, as exemplified by approximately 10% of asymptomatic poultry workers developing anti-H5 antibodies during the 1997 avian influenza epidemic in Hong Kong (7).

We conducted a survey to examine the prevalence of asymptomatic infection by SARS-CoV, manifested as seropositivity to the virus, in a cohort of GPs in Hong Kong, and to identify risk factors for developing it.

MATERIAL AND METHODS

We used a serological and questionnaire survey on GPs in Hong Kong, and letters were sent on 22 May 2003 inviting them to participate in the study. For the private sector, invitations were made to all members of the Hong Kong Doctors Union (HKDU) as well as clients of a local pharmaceutical company. For the public sector, letters were sent to government and university clinics, and individual family physicians. Doctors who for any reason had stopped practising medicine, those practising solely as specialists, dentists, and those who had SARS were excluded.

The study was approved by the ethics committee of Hong Kong Hospital Authority; all study subjects provided written informed consent to participate in the study, and completed a

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self-administered questionnaire. Participants were questioned about their age, gender, clinic location and type, whether they attended as outpatients exclusively, or also as inpatients, whether they had known contact with probable SARS cases and whether they suffered from chronic illness. They were also questioned about the following in the preceding 2 months: average daily number of clinic visits, respiratory illnesses experienced, how often they wore face masks and practised hand washing when seeing patients.

The timing of exposure of participants to SARS-CoV, or whether they have been exposed at all, cannot be known with certainty. Therefore a single blood sample was taken for antibody testing. The blood sample was also tested for complete blood counts, erythrocyte sedimentation rate, liver and renal function tests, creatine phosphokinase level and lactate dehydrogenase level, which may serve to identify associations or risk factors for seropositivity.

Serum samples were tested for SARS-CoV immunoglobulin-G (IgG) antibody with a commercially available whole-virus enzyme linked immunosorbent assay (ELISA) (GBI Biotech, Beijing, China). ELISA positive samples were retested with immunofloresecent antibody (IFA) test. For both tests, samples were tested at serial 2-fold dilutions starting from 1:25 and a titre of 100 was considered positive. ELISA negative samples were not retested because of the anticipated low prevalence of positivity together with a high sensitivity of the test. In an in-house evaluation of the ELISA test kit performed in Princess Margaret Hospital, HKSAR, in May 2003, 65 serum samples taken in 2001–2002 when there was no SARS yielded 2 positives and 63 negatives, giving a specificity of 96.9%. Of 238 serum samples from SARS patients which had been demonstrated to show seroconversion by IFA, there were 228 positives and 10 negatives, giving a sensitivity of 95.8%.

Data were expressed as numbers and proportions. Calculation of 95% CI for proportions was by the exact Clopper-Pearson method. Excel 2000 (Microsoft Inc, WA, USA) was used for data entry and calculations. The study was approved by the ethics committee of Kowloon West Cluster of the Hong Kong Hospital Authority.

RESULTS

From 22 May 2003 to 31 May 2003, approximately 1250 GPs in the private sector who were members of HKDU, approximately 1800 GPs (who did not overlap with HKDU members) from the client base of a local pharmaceutical company, 61 government or university clinics, and 48 individual family physicians in the public sectors were invited to participate in the study. 640 responded. 66 were excluded from the study: 60 did not have blood taken, 2 had overt SARS, 2 were dentists, and 2 had incomplete data which we were unable to obtain. The data of the remaining 574 subjects were analysed.

There were 442 (77%) males and 132 (23%) females. Age range was 25–79 y and median age was 50 y. There was even distribution across age range, clinic location among the 3 major districts of the HKSAR, as well as clinic type (Table I). 148 (26%) attended inpatients as well as outpatients, and the remaining 421 (74%) attended outpatients only. 166 (28.9%) reported definite history of contact with probable SARS cases, the majority of whom were clinic patients (Table II). 164 (28.6%) reported symptoms of upper respiratory tract infection in the preceding 2 months, and 49 (8.5%) had to take leave from work (Table II). During April and May 2003, most respondents (549, 95.6%) wore a face mask whenever they saw patients. In the same period, 240 (42.0%) reported the practice of hand washing after seeing every patient, 257 (45.0%) did so only after seeing febrile patients, and 74 (13.0%) did so only occasionally (Table III).

For the serology tests, 29 samples (5.1%) were tested positive for IgG to SARS-CoV by ELISA. On retesting these samples with IFA, all were negative with a titre of less than 25. The prevalence for seropositivity was thus 0%. Assuming lack of false-negatives for the ELISA test, the sample size of this serological survey ($n = 574$) yielded a 95% confidence interval of 0% to 0.6% for the estimate of seroprevalence of SARS-CoV antibody among the GP population.

Table I. *Distribution of participants by age group, clinic location, and clinic type*

	No. of participants
Age group ($n = 571$)	
25–34	78
35–44	139
45–54	142
55–64	130
65 and over	82
Clinic location ($n = 561$)	
Hong Kong Island	174
Kowloon	208
New Territories	179
Clinic type ($n = 560$)	
Private	481
Street	242
Mall	105
Commercial building	134
Govt. and university clinics	66
Other	13

Table II. *Contact of SARS case and influenza-like illness in the preceding 2 months*

	No. of participants (%)
Contact with SARS case ($n = 574$)	
Positive	166 (28.9)
Clinic patient	121 (21.1)
Hospitalized patient	20 (3.5)
Family member	12 (2.1)
Social contact	26 (4.5)
Other	16 (2.8)
Negative	408 (71.1)
Influenza-like illness ($n = 574$)	
Present	164 (28.6)
Fever	46 (8.0)
Cough	95 (16.6)
Sore throat	100 (17.4)
Leave from work	49 (8.5)
Absent	410 (71.4)

Table III. *Infection control precautions in the preceding 2 months*

	No. of participants (%)
Wearing face mask ($n = 574$)	
Seldom/never	0 (0.0)
Occasionally	11 (1.9)
Whenever seeing febrile patients	14 (2.5)
Whenever seeing patients	549 (95.6)
Hand washing ($n = 571$)	
Seldom/never	0 (0.0)
Occasionally	74 (13.0)
After seeing febrile patients	257 (45.0)
After seeing every patient	240 (42.0)

DISCUSSION

Our study is the first serological survey on SARS-CoV among doctors in the community setting. Of the 574 tested, none showed positive antibodies to SARS-CoV. Thus, although a significant proportion of respondents did report close contact with probable SARS cases in the confines of a clinic, none developed mild or asymptomatic infection by SARS-CoV. The results also show that SARS-CoV was not the causative agent of those who reported having upper respiratory tract infection in the preceding 2 months. Since no participant showed positive antibody to SARS-CoV, we were unable to analyse risk factors for seropositivity as originally planned.

From the data of a manpower survey performed by the Hong Kong Department of Health in y 2000, as well as information from the local pharmaceutical industry, there were approximately 3500 actively practising GPs in Hong Kong in 2003, of which some 90% were in private practice. Although the response rate to our invitation was only around 20%, our study population did constitute about one-sixth of the total workforce. Furthermore, we observed an even distribution of age, gender, practising district, and clinic type among the participants. Thus we believe that our sample is reasonably representative of the overall GP workforce.

Healthcare workers (HCW) represent an at-risk group for contracting SARS. They constituted 22% (386/1755) of all SARS cases reported in Hong Kong and over 98% of them worked in a hospital setting (unpublished data from T. Tsang). The higher risk of SARS faced by hospital HCW may be related in part to the temporal excretion pattern of SARS-CoV in SARS patients. Excretion of SARS-CoV in the respiratory tract peaked about 10 d after disease onset (8), whereas the mean time from onset of clinical symptoms to hospital admission varied between 3 and 5 d (9). Data from Singapore also showed that few secondary cases occur when symptomatic cases are isolated within 5 d of illness onset (10). Other possible factors include prolonged contact with lapses in infection control precautions and the practice of aerosol generating procedures (10). The use of surgical masks, gloves, gowns and the practice of hand washing were shown to be protective of SARS in the hospital setting (11).

The risk of contracting SARS among GPs in the community clinic setting has been less well studied. In Hong Kong, 8 GPs contracted SARS and 4 of them had, during their incubation periods, history of attending to symptomatic patients in their clinics who later were confirmed to have SARS. Although suspicious cases of severe atypical pneumonia retrospectively proven to be SARS began to appear by the end of February 2003, infection control practice continued not to be strictly adopted by HCWs, and certainly by GPs. Even after the World Health Organization issued the global warning on outbreak of severe atypical pneumonia on 12 March 2003, it took some more time before GPs fully realized the need for proper infection control practice in their clinics. It was therefore hardly surprising that 6 of the 8 GPs with SARS had disease onset dates within the period 10 March to 20 March 2003, and none of them had adopted mask wearing and hand washing at the times they were infected. Our questionnaire survey showed that there was a high degree of observance of infection control practices for the latter half of March and throughout April and May. The vast majority of participants in our study (95.6%) reported using face masks whenever seeing patients and 42.0% reported washing hands after seeing every patient. When infection control practice became widely practised, only 2 more GPs contracted SARS in April 2003.

The low seroprevalence of SARS-CoV antibodies in our study population is consistent with studies performed in some other target groups. One such study performed in Princess Margaret Hospital, HKSAR on HCWs who looked after SARS patients there but did not develop SARS, found only 1 with antibody positive to SARS-CoV among 447 tested (unpublished data from T. K. Ng). The positive result came from an asymptomatic nurse who worked in a SARS ward (12). Princess Margaret Hospital was a designated SARS hospital and handled 585 probable SARS cases in the epidemic, and the average exposure level of its staff was likely to be much higher than GPs.

It is worth noting that our study population is not a random sample, so the data are not true prevalence data. Also, sensitivity and specificity data of the serological tests are only preliminary, and the results should be interpreted with discretion.

In conclusion, we have documented the lack of subclinical infection by SARS-CoV among a cohort of GPs in Hong Kong, an at-risk group in the community during a major outbreak of SARS. The finding indicates that the prevalence of such infections among GPs is extremely low and confirms the finding in other studies that infection by SARS-CoV is very likely to be followed by clinical SARS.

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