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SARS transmission in Vietnam outside of the health-care setting

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SUMMARY

To evaluate the risk of transmission of SARS coronavirus outside of the health-care setting, close household and community contacts of laboratory-confirmed SARS cases were identified and followed up for clinical and laboratory evidence of SARS infection. Individual- and household-level risk factors for transmission were investigated. Nine persons with serological evidence of SARS infection were identified amongst 212 close contacts of 45 laboratory-confirmed SARS cases (secondary attack rate 4·2%, 95% CI 1·5–7). In this cohort, the average number of secondary infections caused by a single infectious case was 0·2. Two community contacts with laboratory evidence of SARS coronavirus infection had mild or sub-clinical infection, representing 3% (2/65) of Vietnamese SARS cases. There was no evidence of transmission of infection before symptom onset. Physically caring for a symptomatic laboratory-confirmed SARS case was the only independent risk factor for SARS transmission (OR 5·78, 95% CI 1·23–24·24).

INTRODUCTION

Vietnam was one of the first countries to report an outbreak of atypical pneumonia that later became recognized as Severe Acute Respiratory Syndrome (SARS) and was also the first country to successfully contain SARS and be removed from the World Health Organization list of affected countries [1]. Vietnam suffered a relatively small SARS outbreak, with 63 cases of whom six died [2], which can be traced to the introduction of SARS by a Chinese–American businessman who had stayed on the same hotel floor in Hong Kong as the physician from Guangdong who infected at least 16 guests at the hotel [3]. In common with many outbreaks outside China, the outbreak in Vietnam was largely hospital based but four events involving transmission outside the health-care setting were recognized.

Estimates of the propensity for SARS coronavirus (SARS-CoV) to be transmitted in various settings are important to guide the design of appropriate control measures and to model the impact of various

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interventions on the evolution of an outbreak. A number of authors have used observational data from SARS outbreaks to estimate the average number of secondary cases produced by each case of SARS [4–6]. However, these estimates are averages across large and heterogeneous populations where actual history of exposure to SARS-CoV is unknown and data from a variety of settings are aggregated. These broad estimates need to be supplemented with data from specific settings where exposure to SARS-CoV and behaviours associated with transmission are documented. Such data provide a foundation for the development of evidence-based control measures.

A number of studies have investigated the secondary attack rate of SARS in the community or household setting but the estimates from these studies have been limited by small numbers [7–10], incomplete cohorts [11] or the lack of laboratory confirmation of the primary or secondary SARS cases [12, 13]. We undertook a study of community and household contacts of laboratory-confirmed SARS cases with the primary objective of quantifying the extent of transmission of SARS-CoV using serology to confirm transmission and nasal swabs to detect carriage of SARS-CoV. Secondary objectives were to detect asymptomatic transmission and to investigate individual- and household-level risk factors for transmission.

METHOD

Design and sampling strategy

This is a retrospective study comprised of multiple groups of household and close community contacts of laboratory-confirmed SARS cases.

For analysis purposes laboratory-confirmed SARS cases were divided into 'primary cases' and 'secondary community cases'. A primary case was a case acquired in a hospital setting either in a health-care worker, in-patient or hospital visitor. A secondary community case was defined as a laboratory-confirmed SARS case that was not acquired in a hospital setting. The only exception was the index Vietnam patient, who acquired infection in Hong Kong but was classified as a primary case.

Where a number of SARS cases were known to have a direct community association with one another (excluding hospital contact) the SARS case with the earliest date of onset of symptoms was termed the 'primary case' and was used to define the close community contacts, which would include other SARS cases in the group (secondary community cases).

All persons meeting the definition of a 'close community contact' of a laboratory-confirmed primary case were invited to participate. Close contact occurring in the hospital setting was excluded as this was investigated in a separate study. The definition of close community contact used was:

Any person who had contact with a laboratory-confirmed SARS case from 2 days before the case's symptoms started until the day of hospital admission and the contact comprised:

- living in the same household;

OR

- spending 2 or more hours continuously engaged in face to face contact;

OR

- physically caring for the person in the household setting, regardless of the time involved.

Method of identification of eligible cohort

During the SARS outbreak the Preventive Medical Services compiled detailed contact lists for all probable SARS cases for the purpose of contact tracing and monitoring for signs and symptoms of SARS. All individuals on these contact lists were eligible for a screening interview to see if they met the definition of a close community contact.

SARS cases that were not resident in Vietnam when the study commenced were excluded, as these individuals could not be interviewed to identify close community contacts.

Consent

Written informed consent was obtained for all participants. For those aged <18 years, parental consent was obtained.

Questionnaire

A questionnaire was administered that included questions on household characteristics (e.g. number of rooms and number of occupants); relationship with the SARS case; the type, frequency and duration of contact with the SARS case and history of SARS-compatible illness. The questionnaire also asked about contact with other SARS cases both in the

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community and hospital setting so that these potential confounders could be included in the analysis.

Interviewing

An interviewer training workshop was held. Face-to-face interviews were conducted during weekdays and weekends either in a designated room at one of the participating institutions or in the participant's home.

Biological sampling

All participants were asked for written consent to provide 10 ml of blood in a serum separator tube and a nasal swab specimen (Remel M4RT; Remel Inc., Lenexa, KS, USA). Samples were placed in a cool box prior to transporting to the laboratory on the same day for processing. Nasal swab specimens were frozen the same day at $-80\ ^{\circ}C$ and then thawed once for vortexing and aliquoting into cryovials. Blood specimens were stored at $4\ ^{\circ}C$ prior to centrifugation and aliquoting of serum into cryovials.

All biological samples were drawn from contacts a minimum of 25 days and a maximum of 48 days after last exposure to a SARS case.

Laboratory methods

Each serum sample was tested in a cell lysate ELISA, previously described [14] and in parallel in indirect ELISAs using purified recombinant SARS nucleoprotein expressed from baculovirus. ELISA assays for SARS-CoV detection have good sensitivity and specificity [15, 16] but false-positive results can still occur [17, 18], therefore sera reactive in both ELISAs were then tested in Western blot using SARS antigens and in virus neutralization using Frankfurt SARS strain in Vero E6 cells with an assay similar to that previously described [19]. Sera, which were positive in all assays (ELISA, Western blot and neutralization) were considered seropositive. Sera which were non-reactive in both ELISAs were considered seronegative and not tested further. All sera found to have neutralizing antibody to SARS also showed Western blot reactivity to SARS-specific proteins and similarly, all sera reactive to SARS internal nucleoprotein and SARS spike protein on Western blot also showed reactivity in virus neutralization assays.

A small percentage of screened sera ($\sim 10\%$) were found to be reactive above the cut-off in both cell lysate and recombinant ELISAs but ELISA reactivity was either removed by cross adsorption using cell antigens or was explained by reactivity to either 229E or OC43 human coronavirus proteins on Western blot. Such sera were all considered seronegative. No sera that showed reactivity in ELISAs but lacked SARS-specific Western blot reactivity had SARS-specific neutralizing antibody.

RT–PCR screening for coronavirus was carried out on nasal swab specimens using two separate RT–PCRs with a degenerate primer set to detect all coronaviruses and a SARS- specific PCR reaction based on detection of the nucleocapsid region of the genome [20]. Positive PCR reactions were confirmed by sequencing.

Data entry and analysis

Data were entered into an Epi-Info 6.04d database (CDC, Atlanta, GA, USA) with logical checks and exported into SPSS, version 14 (SPSS Inc., Chicago, IL, USA) for bivariate statistical analysis. The magnitude of association between putative risk factors and SARS-CoV infection was estimated by calculating odd ratios with 95% confidence limits, χ^2 and Fisher's exact tests were undertaken to assess statistical significance of observed associations. To assess the role of confounding, variables with a P value $\leqslant 0{\cdot}2$ in bivariate analysis, gender, and additional variables plausibly associated with household transmission were entered into in a logistic regression model (STATA/SE 8.0; StataCorp., College Station, TX, USA). The initial model employed forward selection with a significance level of $\leqslant 0{\cdot}2$ for inclusion in the model. A final model was achieved by entering only the variables that were retained in the forward selection model. Model fit was assessed using Pearson's goodness-of-fit test and by comparing the model-based results with tabular results using Mantel–Haenszel adjusted odds ratio.

RESULTS

Participation rate

In Vietnam between 26 February and 28 April 2003 a total of 63 cases met the WHO case definition for a probable SARS case and had laboratory evidence of infection with SARS-CoV by either PCR, serology or both. All 63 cases were included as the study base and of these, 53 were identified as 'primary cases' comprising one index case, 37 health-care

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Table 1. *Contact group characteristics*

Group no.	*n*	Swab given		Blood sample given		Gender		Age (years)	
		Yes	%	Yes	%	Female	%	Median	Mean
1	3	3	100	3	100	1	33	27	31
2	3	3	100	3	100	2	67	50	51
3	7	7	100	7	100	4	57	23	26
4	6	5	83	4	67	3	50	27	28
5	4	4	100	4	100	2	50	17	20
6	3	3	100	3	100	1	33	18	27
7	2	2	100	2	100	1	50	21	21
8	6	6	100	6	100	2	33	24	31
9	8	8	100	6	75	5	63	13	20
10	3	3	100	2	67	1	33	30	28
11	1	1	100	0	0	1	100	49	49
12	1	1	100	1	100	1	100	32	32
13	3	1	33	2	67	1	33	9	16
14	4	4	100	4	100	1	25	32	36
15	2	2	100	2	100	1	50	74	74
16	4	4	100	4	100	2	50	45	43
17	2	2	100	2	100	1	50	35	35
18	5	5	100	5	100	2	40	34	28
19	5	5	100	5	100	3	60	16	28
20	3	3	100	3	100	1	33	20	26
21	3	3	100	3	100	1	33	16	22
22	1	1	100	1	100	1	100	65	65
23	13	12	92	2	15	8	62	26	24
24	1	0	0	0	0	1	100	32	32
25	1	1	100	1	100	0	0	26	26
26	8	8	100	7	88	5	63	20	25
27	7	7	100	7	100	3	43	35	40
28	2	2	100	2	100	2	100	52	52
29	2	2	100	2	100	1	50	37	37
30	6	6	100	5	83	3	50	43	45
31	6	6	100	4	67	1	17	21	25
32	11	11	100	8	73	8	73	26	24
33	1	1	100	1	100	1	100	28	28
34	3	3	100	3	100	1	33	28	27
35	4	4	100	3	75	2	50	43	37
36	7	7	100	5	71	4	57	19	35
37	1	1	100	1	100	0	0	22	22
38	3	3	100	2	67	3	100	10	18
39	3	3	100	3	100	1	33	19	25
40	5	5	100	5	100	3	60	45	38
41	1	1	100	1	100	1	100	18	18
42	4	4	100	3	75	2	50	33	39
43	4	4	100	3	75	2	50	45	39
44	4	4	100	4	100	2	50	38	39
45	36	36	100	36	100	18	50	44	43
Total	212	207	98	180	85	110	52	30	33

workers, seven in-patients and eight hospital visitors thought to have acquired infection by visiting the affected hospital. The close contacts of 45 of the 53 'primary cases' (85%) were included in the study. Of the seven who were not included, three were expatriate doctors for whom community contacts could not be identified as they had left Vietnam by the time contact tracing began and four either refused to participate or could not be traced at the time of the study.

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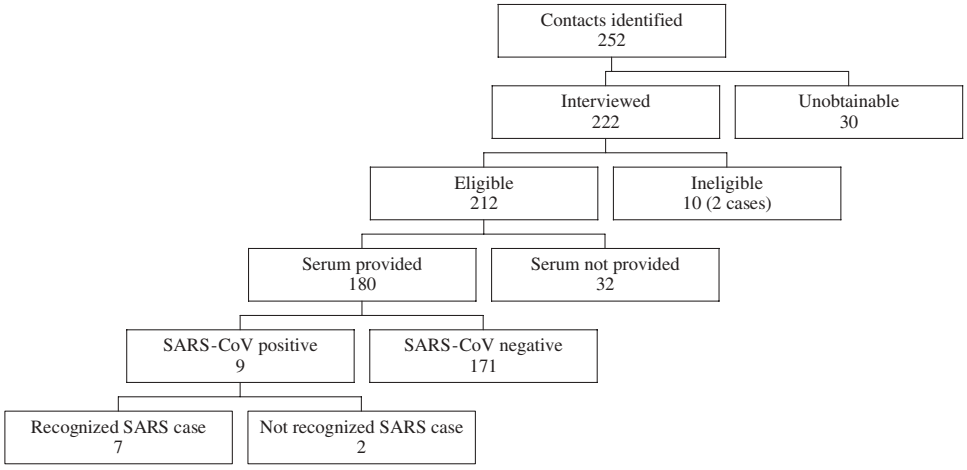

Fig. Primary community clusters, participation rate.

A total of 252 close contacts were identified for these 45 primary cases, of which 222 (88%) completed a questionnaire. Information was not available on the 30 contacts who could not be included in the study so it was not possible to compare the characteristics of non-responders and responders. Ten of the contacts interviewed did not meet the contact definition, leaving a total of 212 contacts.

Of the 212 eligible contacts, 207 (98%) provided a nasal swab and 180 (85%) provided a blood sample. The median age of the 212 contacts was 32·7 years (range 2 months to 82 years) and 52% were female. The 32 individuals from whom a blood sample was not obtained were on average younger than the 180 who provided a blood sample (median age 8 *vs.* 32 years, Mann–Whitney U test $P<0{\cdot}001$).

Contact group characteristics

The characteristics of the 45 contact groups of the primary cases are shown in Table 1. The mean number of contacts was five persons (range 1–36).

Attack rates

None of the contacts who provided a nasal swab ($n=207$) were PCR positive for SARS-CoV. One individual, a male aged 43, was PCR positive for coronavirus OC43. This person did not report any illness and was classified SARS-CoV negative.

Nine contacts had serological evidence of SARS-CoV infection of which seven were clinical cases of SARS recognized during the outbreak (Fig.). In addition, one person, who reported a headache and cough but no fever, was reactive to SARS-CoV in ELISA but was also reactive to OC43 proteins in Western blot and was, therefore, not considered a SARS case.

In total 5% (9/180) of contacts had serological evidence of infection, and assuming the 32 contacts who failed to provide a sample were negative for SARS-CoV, then 4·2% (95% CI 1·5–7) were infected. In this study, the average number of secondary infections caused by a single infectious case (the basic reproduction number) was 0·2. The nine secondary SARS cases occurred in three of the 45 contact groups, giving a contact group attack rate of 6·7% (95% CI −0·6 to 14).

For the 45 confirmed SARS cases included in this study, the mean time from onset of symptoms to hospital admission was 4 days (range 0–13). For the three SARS cases that caused secondary cases in the community the average interval from onset of symptoms to hospital admission was 6 days.

Of the two people that had evidence of SARS-CoV infection but were not clinically recognized SARS cases, one reported only myalgia and fever but no respiratory symptoms in the period from 2 days before onset of illness in the primary case until 2 weeks after the case was admitted to hospital.

All of the nine secondary cases were adults who reported direct contact with a laboratory-confirmed SARS case whilst that case was sick. Fifty-three individuals reported contact with a case in the 2 days preceding onset of symptoms in the case but no contact with the case whilst the case was ill. None of

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Table 2. *Single variable analysis of individual-level factors associated with transmission of SARS-CoV*

Factor	Non-cases	Cases	OR (95% CI)	*P* value Fisher's exact test
Gender				
Male	85	3	1	
Female	86	6	1·98 (0·42–10·35)	0·50
Age, years (mean)	34·5	38·3		0·4*
Relationship				
Non-relative	34	2	1	
Relative	137	7	0·87 (0·15–6·4)	1
Live in same house as case				
No	51	6	1	
Yes	120	3	0·21 (0·04–1·01)	0·03
Physically cared for case				
No	120	3	1	
Yes	51	6	4·71 (0·99–24·86)	0·03
Contact in the case's house				
No	15	2	1	
Yes	156	7	0·34 (0·06–2·58)	0·2
Ate in same room as case†				
Never	57	3	1	
Sometimes/Often	99	4	0·77 (0·14–4·51)	0·7
Slept in same room as case†				
Never	116	6	1	
Sometimes/Often	40	1	0·48 (0·02–4·27)	0·68
Bathed case†				
Never	149	7	1	
Sometimes/Often	7	0	0 (0–20·93)	1
Wash case's clothes†				
Never	128	5	1	
Sometimes/Often	28	2	1·83 (0·23–11·49)	0·61
Longest period in same room as case†				
0–4 h	104	5	1	
⩾5 h	52	2	0·8 (0·1–4·88)	1
Wore mask during contact with case†				
Never	147	7	1	
Sometimes/most times	9	0	0 (0–15·37)	1
Visited case in hospital†				
No	87	2	1	
Yes	69	5	3·15 (0·52–24·27)	0·25
Pre-existing chronic illness				
No	149	7	1	
Yes	22	2	1·93 (0·26–11·24)	0·3
Smoking				
Never smoked	129	7	1	
Current smoker	33	0	0 (0–3·26)	0·35

OR, Odds ratio; CI, confidence interval.
* Mann–Whitney *U* test.
† Of those who reported contact in household ($n = 163$).

these 53 people had evidence of SARS-CoV exposure. Therefore, there was no evidence of transmission occurring before symptom onset.

Two of the 10 community contacts that did not meet the study definition for a close contact were actually laboratory-confirmed SARS cases themselves. One

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Table 3. *Multivariate analysis of individual-level factors associated with transmission of SARS-CoV*

Variable	OR	95% CI	*P* value
Physically cared for case	5·78	1·23–24·24	0·022
Lived in same house as case	0·18	0·04–0·78	0·022

Likelihood ratio $P=0{\cdot}005$; Pearson's goodness-of-fit test $P=0{\cdot}2$.

of these cases only had contact with a SARS case in a hospital setting and the other was a work colleague of a confirmed case but denied face-to-face contact of two or more hours.

Factors associated with individual risk of infection

In the bivariate analysis only two factors, living in the same household as the primary case and physically caring for the primary case, were statistically associated with transmission of SARS-CoV (Table 2). Living in the same household as the case was associated with a reduced risk of SAR-CoV transmission but, as discussed later, this result probably represents a selection bias. The forward selection logistic regression model also retained only these two variables, which were then entered into the final model (Table 3).

Ninety-five percent of contacts reported never wearing a mask during contact with the SARS case.

Factors associated with risk of transmission in the household

Of the 45 contact groups of the primary cases, evidence of transmission was identified in three groups (contact group numbers 1, 16, 45). Table 4 shows the contact history of the nine people with evidence of SARS-CoV exposure. Because exposure to the primary case occurred in multiple locations, it was not possible to ascertain where transmission occurred. However, if it is assumed that for contact groups 16 and 45 transmission occurred in the household (home or hotel), then risk factors for transmission associated with household characteristics (e.g. number of rooms) can be examined. None of the household characteristics included in the study were statistically associated with the risk of household transmission.

DISCUSSION

In this series of 45 laboratory-confirmed SARS cases there was limited community transmission despite unprotected contact; with each infectious case causing on average only 0·2 secondary infections. It has been estimated that, at a population level, one SARS case will result in around three new cases [4, 5] but it seems that the risk of community transmission is generally much lower than this. It is, however, not possible to assess this accurately as behaviour changes may occur rapidly as an epidemic evolves. Other studies of the risk of transmission of SARS in the community setting have also found that most SARS patients do not easily transmit infection prior to hospitalization, with transmission rates ranging between 0% and 10% [7, 8, 10, 12, 13, 21–24]. The reason that hospital transmission is more common than community transmission seems to relate primarily to three factors: the temporal profile of viral excretion, which peaks at around day 11 [25]; the patient profile of viral excretion, which seems to be greater in sicker patients [26]; and the predominant transmission route, which is probably large respiratory droplets, requiring intimate contact with sick patients or the handling of infectious secretions.

Respondents in this study were asked about the frequency of sleeping and eating in the same room as the case, the duration of time spent in the same room as the case and the frequency of washing the case's clothes or sheets, but none of these factors were associated with transmission. The finding that 'physically caring' for a symptomatic case was the only factor associated with transmission would support transmission predominantly by large respiratory droplets with limited ability for transmission by environmental contamination, fomites or aerosolization. Although data have been published to suggest airborne transmission of SARS, this would appear to be an unusual event [27]. There have been no conclusive reports of transmission occurring from SARS cases in the pre-symptomatic phase and we also found no evidence of transmission occurring prior to onset of symptoms [23, 28].

The reason that in our study household members were statistically less likely to be infected than non-household contacts is probably a result of selection bias, with under-ascertainment of non-affected, non-household contacts.

Two sub-clinical SARS infections were identified in this study, representing 3% (2/65) of all SARS cases in Vietnam. Mild and asymptomatic SARS cases have been recognized [29–34] and they have been reported as being rare [11, 35]. It would seem, however, that whilst the absolute risk of sub-clinical

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Table 4. *Contact history of secondary community cases*

Secondary case no.	Contact group no.	Recognized SARS case	Sites of contact with primary case				
			Home	Hotel	Office	Car	Hospital
1	1	No			Yes		Yes
2	16	Yes		Yes		Yes	No
3	16	Yes		Yes		Yes	Yes
4	16	Yes		Yes		Yes	No
5	16	Yes				Yes	No
6	45	No	Yes				Yes
7	45	Yes	Yes				Yes
8	45	Yes	Yes				Yes
9	45	Yes	Yes				Yes

cases is low; as a proportion of all transmission events sub-clinical infection is not uncommon, although the spectrum of disease might vary with infecting SARS-CoV strain [11]. Chang *et al*. found one asymptomatic case and two mild cases amongst nine SARS-CoV antibody-positive health-care workers [30]. Whilst Ho *et al*. did not identify any asymptomatic cases, two mild cases were found amongst eight SARS-CoV antibody-positive health-care workers [31]. Chen *et al*. found a positive seroprevalence of only 0·4% in asymptomatic health-care workers exposed to SARS patients but in a total cohort of 1147 health-care workers, 14% (15/105) of all SARS infections were asymptomatic [36]. Wilder-Smith *et al*. found mild or asymptomatic infection in 10% (8/80) of exposed health-care workers, representing 18% (6/45) of all SARS infections [37]. Reassuringly, there was no evidence of onward transmission from the two unrecognized infections identified in our study, despite the absence of quarantine for these individuals. This suggests that sub-clinical cases are not important in terms of sustaining transmission.

It seems that the risk of transmission of SARS is very variable with most cases infecting few people and a few cases infecting many [11, 38]. Therefore, the reliability of transmission studies will be affected by the inclusion or exclusion of the few individuals that lie at the extreme. Seventy-one percent (45/63) of all SARS cases in Vietnam and 84% (212/252) of their close contacts were included in this study, making it one of the most comprehensive studies undertaken of SARS transmission outside of the health-care setting. Only three of the four Vietnam SARS cases known to have seeded secondary community cases were included in the study. The case that is not included was the source of three other confirmed cases outside Vietnam [39] and therefore the results presented here may be an underestimate of the community transmission risk.

The finding of cross-reactivity between OC43 and SARS-CoV ELISAs in one individual indicates that analysis of SARS-CoV serology requires careful interpretation and indicates that ELISA screening should be supplemented with additional tests to verify specificity of SARS ELISA reactivity, especially in the absence of a clinically compatible illness. However, it is unlikely that any of the secondary transmissions identified in this study are false-positive results since the specimens were all positive using four different assays; two different ELISAs, Western blot and neutralizing antibody, and cross-reactivity to human coronaviruses 229E or OC43 was also investigated and found to be absent. It is possible that there are false-negative results but samples were taken a minimum of 25 days and a maximum of 48 days after last exposure to a SARS case, so a detectable antibody response would be expected at this stage in most infected persons [40, 41].

Lipsitch *et al*. have demonstrated how the interval from onset of symptoms to isolation affects the secondary transmission rate of SARS [4] and our data agree very well with this observation, that isolation of symptomatic cases is a critical control measure and that the risk of secondary transmission rises once the interval from onset of symptoms to isolation increases above 4 days. In conclusion, the overall risk of community transmission of SARS is low, generally requires intimate and unprotected contact with an ill SARS case and can be further minimized by rapid isolation of symptomatic cases. However, notable and well publicized exceptions to this rule include the index case in Hong Kong and

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the Amoy Gardens outbreak. Predicting which SARS cases will be the exception is not possible, so all must be treated with great caution.

APPENDIX. The WHO SARS Investigation Team in Vietnam

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Anon.** Severe Acute Respiratory Syndrome (SARS) – Multi-country outbreak – update 41, 28 April 2003, World Health Organization (http://www.who.int/csr/don/2003_04_28/en/). Accessed 11 October 2004.
2. **Vu HT, *et al.*** Clinical description of a completed outbreak of SARS in Vietnam, February–May 2003. *Emerging Infectious Diseases* 2004; **10**: 334–338.
3. **Anon.** Update: outbreak of severe acute respiratory syndrome – worldwide, 2003. *Morbidity and Mortality Weekly Report* 2003; **52**: 241–246, 248.
4. **Lipsitch M, *et al.*** Transmission dynamics and control of severe acute respiratory syndrome. *Science* 2003; **300**: 1966–1970.
5. **Riley S, *et al.*** Transmission dynamics of the etiological agent of SARS in Hong Kong: impact of public health interventions. *Science* 2003; **300**: 1961–1966.
6. **Wallinga J, Teunis P.** Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *American Journal of Epidemiology* 2004; **160**: 509–516.
7. **Peck AJ, *et al.*** Lack of SARS transmission and U.S. SARS case-patient. *Emerging Infectious Diseases* 2004; **10**: 217–224.
8. **Isakbaeva ET, *et al.*** SARS-associated coronavirus transmission, United States. *Emerging Infectious Diseases* 2004; **10**: 225–231.
9. **Lee CC, *et al.*** Seroprevalence of SARS coronavirus antibody in household contacts. *Epidemiology and Infection* 2005; **133**: 1119–1122.
10. **Xie SY, *et al.*** Serological investigation on close contacts to patients with severe acute respiratory syndrome in an SARS outbreak. *Zhonghua Liu Xing Bing Xue Za Zhi* 2004; **25**: 867–869.
11. **Leung GM, *et al.*** SARS-CoV antibody prevalence in all Hong Kong patient contacts. *Emerging Infectious Diseases* 2004; **10**: 1653–1656.
12. **Lau JT, *et al.*** Probable secondary infections in households of SARS patients in Hong Kong. *Emerging Infectious Diseases* 2004; **10**: 235–243.
13. **Goh DL, *et al.*** Secondary household transmission of SARS, Singapore. *Emerging Infectious Diseases* 2004; **10**: 232–234.
14. **Kuiken T, *et al.*** Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *Lancet* 2003; **362**: 263–270.
15. **Chan PK, *et al.*** Immunofluorescence assay for serologic diagnosis of SARS. *Emerging Infectious Diseases* 2004; **10**: 530–532.
16. **Woo PC, *et al.*** Relative rates of non-pneumonic SARS coronavirus infection and SARS coronavirus pneumonia. *Lancet* 2004; **363**: 841–845.
17. **Wang Y, *et al.*** Cross-reaction of SARS-CoV antigen with autoantibodies in autoimmune diseases. *Cell Molecular Immunology* 2004; **1**: 304–307.
18. **Woo PC, *et al.*** False-positive results in a recombinant severe acute respiratory syndrome-associated coronavirus (SARS-CoV) nucleocapsid enzyme-linked immunosorbent assay due to HCoV-OC43 and HCoV-229E rectified by Western blotting with recombinant SARS-CoV spike polypeptide. *Journal of Clinical Microbiology* 2004; **42**: 5885–5888.
19. **Gao W, *et al.*** Effects of a SARS-associated coronavirus vaccine in monkeys. *Lancet* 2003; **362**: 1895–1896.
20. **Bermingham A, *et al.*** Laboratory diagnosis of SARS. *Philosophical Transactions of the Royal Society of London, B: Biological Sciences* 2004; **359**: 1083–1089.
21. **Avendano M, Derkach P, Swan S.** Clinical course and management of SARS in health care workers in Toronto: a case series. *Canadian Medical Association Journal* 2003; **168**: 1649–1660.
22. **Anon.** SARS outbreak in the Philippines. *Weekly Epidemiological Record* 2003; **78**: 189–96. (http://www.who.int/wer/2003/en/wer7822.pdf).
23. **Anon.** Efficiency of Quarantine During an Epidemic of Severe Acute Respiratory Syndrome – Beijing, China,

2003. *Morbidity and Mortality Weekly Report* 2003; **52**: 1037–1040.

24. **Yu WC, *et al.*** Prevalence of subclinical infection by the SARS coronavirus among general practitioners in Hong Kong. *Scandinavian Journal of Infectious Diseases* 2004; **36**: 287–290.
25. **Chan KH, *et al.*** Detection of SARS coronavirus in patients with suspected SARS. *Emerging Infectious Diseases* 2004; **10**: 294–299.
26. **Chu CM, *et al.*** Initial viral load and the outcomes of SARS. *Canadian Medical Association Journal* 2004; **171**: 1349–1352.
27. **Yu IT, *et al.*** Evidence of airborne transmission of the severe acute respiratory syndrome virus. *New England Journal of Medicine* 2004; **350**: 1731–1739.
28. **Li HL, *et al.*** Epidemiological investigation of nosocomial infection of SARS in medical staff of a hospital. *Di Yi Jun Yi Da Xue Xue Bao* 2004; **24**: 355–358.
29. **Lee HK, *et al.*** Asymptomatic severe acute respiratory syndrome-associated coronavirus infection. *Emerging Infectious Diseases* 2003; **9**: 1491–1492.
30. **Chang WT, *et al.*** SARS exposure and emergency department workers. *Emerging Infectious Diseases* 2004; **10**: 1117–1119.
31. **Ho KY, *et al.*** Mild illness associated with severe acute respiratory syndrome coronavirus infection: lessons from a prospective seroepidemiologic study of health-care workers in a teaching hospital in Singapore. *Journal of Infectious Diseases* 2004; **189**: 642–647.
32. **Li G, *et al.*** Mild severe acute respiratory syndrome. *Emerging Infectious Diseases* 2003; **9**: 1182–1183.
33. **Ip M, *et al.*** Seroprevalence of antibody to severe acute respiratory syndrome (SARS)-associated coronavirus among health care workers in SARS and non-SARS medical wards. *Clinical Infectious Diseases* 2004; **38**: e116–118.
34. **Yu F, *et al.*** Evaluation of inapparent nosocomial severe acute respiratory syndrome coronavirus infection in Vietnam by use of highly specific recombinant truncated nucleocapsid protein-based enzyme-linked immunosorbent assay. *Clinical and Diagnostic Laboratory Immunology* 2005; **12**: 848–854.
35. **Chan PK, *et al.*** Severe acute respiratory syndrome-associated coronavirus infection. *Emerging Infectious Diseases* 2003; **9**: 1453–1454.
36. **Chen WQ, *et al.*** Anti-SARS-CoV immunoglobulin G in healthcare workers, Guangzhou, China. *Emerging Infectious Diseases* 2005; **11**: 89–94.
37. **Wilder-Smith A, *et al.*** Asymptomatic SARS coronavirus infection among healthcare workers, Singapore. *Emerging Infectious Diseases* 2005; **11**: 1142–1145.
38. **Dye C, Gay N.** Epidemiology. *Modeling the SARS epidemic*. *Science* 2003; **300**: 1884–1885.
39. **Desenclos JC, *et al.*** Introduction of SARS in France, March–April, 2003. *Emerging Infectious Diseases* 2004; **10**: 195–200.
40. **Nie Y, *et al.*** Neutralizing antibodies in patients with severe acute respiratory syndrome-associated coronavirus infection. *Journal of Infectious Diseases* 2004; **190**: 1119–1126.
41. **Chen W, *et al.*** Antibody response and viraemia during the course of severe acute respiratory syndrome (SARS)-associated coronavirus infection. *Journal of Medical Microbiology* 2004; **53**: 435–438.