Infectivity of Severe Acute Respiratory Syndrome during Its Incubation Period

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Objective To evaluate the infectivity of severe acute respiratory syndrome (SARS) during its incubation period by investigating chains of transmission and individuals isolated for medical observation with a view to providing scientific evidence for updating protocols of medical isolation. **Methods** Individuals related with the two SARS chains of transmission in Beijing in 2003 and a group of individuals isolated for medical observation in Haidian district of Beijing during the SARS outbreak were selected as subjects of study. Contactors with SARS patients and those with symptom development following the contacts were investigated via questionnaire. Serum samples were collected from super transmitters and tested for SARS-CoV antibody by neutralization test and enzyme linked immunosorbent assay (ELISA). **Results** A total of 1 112 contactors were investigated in three surveys. Of them, 669 had a history of close contact with symptomatic SARS patients, 101 developed symptoms with a rate of 15.1%, 363 had a history of close contact with patients in their incubation period, none of whom developed symptoms (0%). Serum samples were collected from 32 highly-exposed individuals, of whom 13 developing SARS symptoms after contact had serum samples positive for SARS-CoV antibody. Samples collected from the asymptomatic contactors were all negative for SARS-CoV antibody. **Conclusion** SARS cases are infectious only during their symptomatic period and are non-infectious during the incubation period. Isolation for medical observation should be placed for individuals who are in close contact with symptomatic SARS patients. The results of our study are of decisive significance for the Ministry of Health to the definition of SARS close contactor.

Key words: Severe acute respiratory syndrome; Chain of transmission; Incubation period; Symptomatic period; Infectivity

INTRODUCTION

Severe acute respiratory syndrome (SARS) struck humanity all of a sudden in 2003. Beijing was one of the areas suffering worst from its outbreak[1], which yet offers a best field for epidemiological studies of SARS. In identifying the common feature of SARS transmission, evaluating the infectivity of SARS cases during their incubation period, and providing scientific information for the development of guideline for isolation for medical observation, we undertook detailed epidemiological surveys regarding the chains of transmission triggered by super transmitters A and C in Beijing, performed serum antibody testing with samples from some close contactors, and surveyed the contact and conditions of developing symptoms in the individuals isolated for medical observation in Haidian district of Beijing during the epidemic. Results of the comprehensive analyses of data collected from the three independent surveys are presented as below.

MATERIALS AND METHODS

Subjects

Subjects of epidemiological survey included all SARS cases in the outbreak, chains of transmission triggered by cases C and A, individuals in close contact with them within four days prior to illness

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onset, and 1 028 individuals isolated for medical observation in Haidian district of Beijing by May 23, 2003.

Subjects of serological study included medical workers and family members involved in management of the two super transmitters (case C and one severe secondary case) without precautions during the early SARS outbreak stage with case C as an index case; among these subjects some progressed into SARS, while the others did otherwise.

Methods

Case diagnosis. The diagnosis of clinical SARS cases was made according to the clinical criteria for severe acute respiratory syndrome issued by the Ministry of Health, People's Republic of China in 2003[2]. The index case was retrospectively diagnosed following the epidemiological survey.

Confirmation with laboratory examination. Clinical SARS cases were confirmed by neutralization test, and serum samples were found positive for SARS-CoV antibody.

Definitions in this study. ① Super transmitter was defined as the SARS case who directly or indirectly infected more than 10 cases by one or more generations in the same transmission chain. ② Close contactors were defined as individuals who had face to face contact with SARS cases within four days before the onset of the symptoms (average incubation period) and the time when the isolated treatment was started, as well as individuals providing medical and nursing care, visitors, and those exposed to their secretions or body fluids. Close contactors were subdivided into two groups: one having contacts with SARS cases in the incubation period and the other doing so in the symptomatic period based on their times of contact. ③ Close contactors in the incubation period were defined as individuals in close contact with SARS cases without precautions within four days prior to the emergence of symptoms. ④ Close contactors in the symptomatic period were defined as individuals in close contact with SARS cases without precautions shortly prior to the time of illness onset or death or during the course of isolation.

Methods of Epidemiological Survey

Survey questionnaires were designed for both SARS cases and contactors. A retrospective survey was employed to investigate relevant individuals one by one. A sampling survey was conducted for the individuals isolated for medical observation in Haidian district.

Survey of transmission chain. Information was collected by medical record review, and face-to-face and telephone interview. With cases C and A as two index cases, their secondary generations, close contactors and informants were surveyed individually in detail following the clues provided by their family members. Contact history and symptom development of the contactors were recorded in detail. Those left without symptom filled in the contactor survey questionnaire. Relation with the index case, times and routes of contact within four days prior to hyperthermia, and the time when a proper treatment was initiated for each contactor in close contact with SARS, were determined by the known average incubation period of SARS[3] with their disease outcomes monitored.

Survey of isolated individuals. Haidian district is geographically divided into eastern, western, southern, northern and central sections. One neighborhood (residential community) where a cluster of residents were isolated for medical observation was selected in each section. The universal questionnaires were distributed to individuals isolated for medical observation by the Neighborhood Committee and subjects for medical observation were selected by the SARS Prevention and Treatment Office under the Committee. The surveyed individuals themselves filled in the questionnaire. In case the subject was unable to fill in the questionnaires by himself/herself, another individual was appointed on his/her behalf.

Methods of Serological Examination

Following the principle of voluntary testing, a venous blood sample (10 mL) was taken from each close contactor with cases C and Z, two super transmitters in the chain of transmission triggered by case C. Sera were separated. Each sample was tested by neutralization test and ELISA for SARS-CoV antibody.

Analytic Methods

Plotting diagrams of transmission chains. Diagrams of the transmission chains were plotted following the two lines of family and hospital. Subsequent illness onset of contactors with different generations of cases were calculated.

Plotting diagrams of contact history analyses. Contactors involved in the surveys were divided into symptomatic and asymptomatic groups, based on their infection outcomes. Diagrams of contact history analysis were plotted for each group. The diagram had a horizontal axis with the day when hyperthermia of the SARS case started as day 0, and the bar shadow perpendicular to the horizontal axis was drawn for the day. Values for each day before hyperthermia were minus, marked with days 1, 2, 3,

and 4. Otherwise the values were positive, marked with days 1, 2, and 3. A line was drawn for each contactor between the starting and end points of contact with his or her previous generation of the infected.

Infectivity analysis. The secondary attack rate via contact was calculated for each close contactor based on the time of hyperthermia occurrence while having contact with SARS cases.

RESULTS

SARS Transmission Chain with Case C as an Index Case

A total of 207 close contactors related with the transmission chain were identified in the epidemic. With case C as the first generation, 37 cases of four generations were found, of which two generations emerged in the family transmission chain with 13 secondary cases and one death, and three generations emerged in the hospital transmission chain with 23 secondary cases without death. Thirty-two individuals had direct contact with case C, 12 of whom had developed symptoms. Sixty-six individuals had direct contact with the second generation of case Z (a male patient with cerebral infarction in the same ward beside with case C, at the age of 88 years), 13 of whom became symptomatic. The two super transmitters were the elderly with cerebral infarction. A large number of individuals were involved in close contacts during emergency management, nursing care and visits. The transmission process of the entire outbreak could be portrayed with a clear transmission chain (Fig. 1).

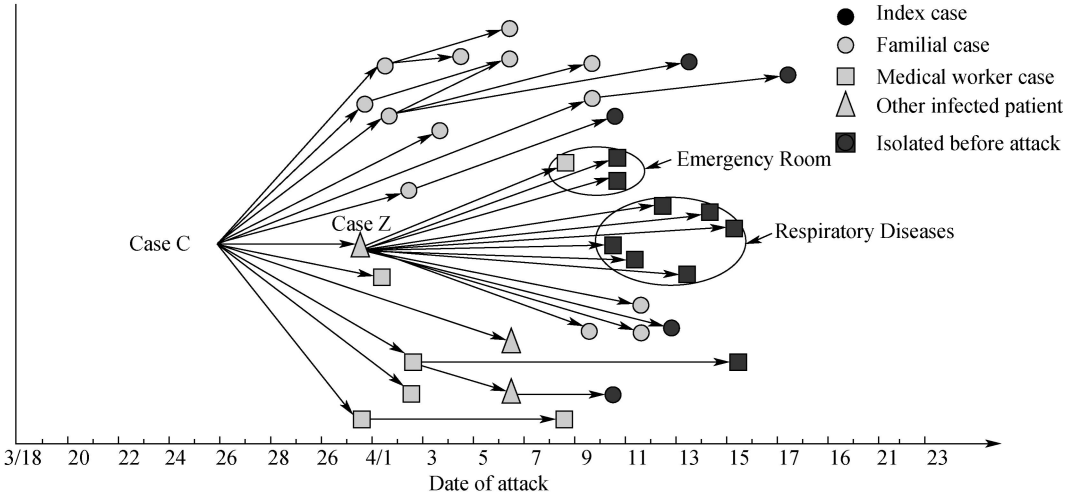

FIG. 1. Transmission chain of SARS outbreak with case C as an index case in March-April, 2003.

Serum samples were collected from 32 individuals in close contact with the super transmitter during the symptomatic period. Of them, 19 did not progress into SARS cases following the contacts 16 were left without symptoms, 1 experienced sore throat and 2 experienced sore throat and diarrhea in 12 days after the contact. All these cases had their symptoms disappeared without treatment, or alternatively none of them progressed into SARS cases. Of the tested contractors, 13 progressed into SARS cases subsequently. Neutralization test and ELISA showed that 19 serum samples from asymptomatic close contactors were negative for SARS-CoV-specific antibody, while 13 samples from secondary SARS cases were positive for SARS-CoV-specific antibody. The neutralizing antibody titer was 1:43 at week 22 after the onset of illness.

A total of 207 individuals in close contact with SARS cases in the epidemic were identified. The close contactors were divided into two groups. Those in group 1 had contact only during the incubation period and those in group 2 had contact during the symptomatic period (including those who had contact before and in the symptomatic period and those who had contact only during the symptomatic period). Close contactors in the incubation period included 82 persons who were free of symptoms. Of the 125 close contactors in the symptomatic period, 36 (28.8%) progressed into SARS with one dead (Table 1).

TABLE 1

Secondary Morbidity Rate among Contactors in Transmission Chain with Case C as an Index Case

Period	Asymptomatic Cases (*n*)	Symptomatic Cases (*n*)	Total
Incubation Period	82	0	82
Symptomatic Period	89	36	125
Total	171	36	207

Main ways of contact during the incubation period included living together (38 persons, accounting for 46.3%), working together (15 persons, accounting for 18.3%), and staying in the same classroom (35.4%). None of them developed symptoms.

In the close contacts with SARS cases in the symptomatic period, the most risk factors were the emergency treatment, operation of the respirator, nursing care and sleeping in the same room when the patient had no precautions, followed by staying in the same ward, visiting the patient in hospital, contacting the patient's secretions and routine nursing care (Table 2).

All the 36 secondary SARS cases in our study had a history of close contact with cases of previous generation in the symptomatic period. No symptom occurred in 15 employees working at the same counter and in 29 students studying in the same classroom in the incubation period, and 38 family members having close contact with medical workers before or in the early stage of their illness onset. The close contactors, involved in the familiar transmission chain, were divided into symptomatic group and asymptomatic group based on their infection outcomes. Analytic diagrams on contact history were plotted according to their times of contact (Fig. 2).

TABLE 2

Symptom Development due to Contact in the Symptomatic Period in Transmission Chain with Case C as an Index Case (*n*=125)

Ways of Contact	Contactors [(*)] (*n*)	Morbidity Rate (%)
Hospital Transmission	**103**	**23**
Non-medical Workers	**36**	**25**
Patients in Same Ward	10	20
Patients in Different Wards	9	11
Accompanying Patient	12	42
Visiting Patient	5	20
Medical workers	**67**	**22**
ICU Treatment, Respirator Operation	15	80
Contact with Secretions or Body Fluids	22	9.1
Routine Medical Care	30	3.3
Familial Transmission	**22**	**59**
Accompanying and Caring for Patient	10[(**)]	80
Living Together	5[(**)]	80
Visit	5	20
Daily Life	2	0

Note. *Close contactors during the symptomatic period, **one individual accompanying the patient and sleeping in the same room did not experience any attack.

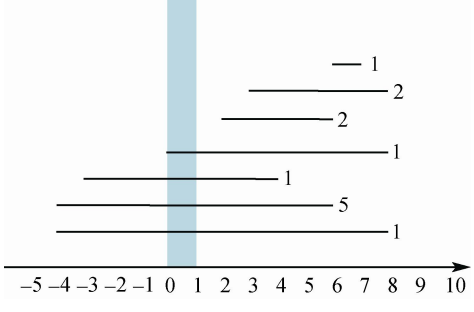

FIG. 2-1. Times of contact with SARS cases.

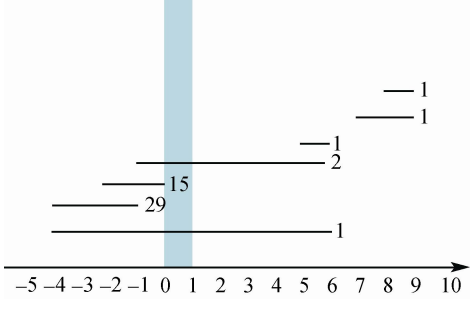

FIG. 2-2. Times of contact with close contactors.

As Fig. 2 indicates, all the 13 cases had contact with cases of the previous generation, 85% of the cases had their contact within 3-5 days after the onset of hyperthermia symptoms, and the morbidity rate among the contactors was 70% and 67%, respectively ($P<0.05$). Fifty contactors displayed no symptom. Of them, 44 (88%) had contact with SARS cases during the incubation period.

SARS Outbreak Transmission Chain with Case A as an Index Case

With case A as the first generation and the directly infected cases as the second generation, four generations of 42 cases were monitored in the outbreak. Of the cases, 9 had direct contact with case A, 9 developed symptoms, and 2 died. A total of 230 direct contactors were identified as the third generation. Of the contactors, 30 developed symptoms, and 4 died. Of the 26 cases having direct contact with case A's wife, 19 were symptomatic and 1 died. Of the 30 individuals in direct contact with cases A's son, 4 were symptomatic. Of the 42 in direct contact with the elevator operator serving case A, 7 were symptomatic and 3 died. As for the 37 direct contactors of the third generation, 3 survived without any symptom due to their isolation from the contactors. The illness onset in different generations and the transmission relations are shown in Fig. 3.

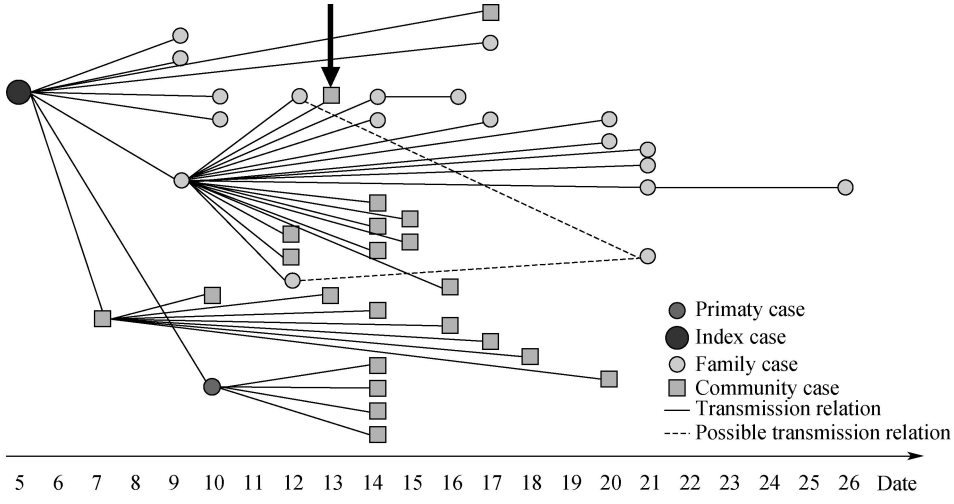

FIG. 3. Transmission chain of SARS outbreak with case A as an index case in 2003, 4.

A total of 275 close contactors were identified in the epidemic. Of the 114 close contactors in the incubation period, none developed symptoms. Of the 161 having contact in the symptomatic period, 41 were symptomatic and 5 (12.2%) died (Table 3).

TABLE 3

Secondary Morbidity Rate among Contactors with Case A as an Index case in the Incubation and Symptomatic Period

Period	Asymptomatic Cases (*n*)	Symptomatic Cases (*n*)	Total
Incubation Period	114	0	114
Symptomatic Period	120	41*	161
Total	234	41	275

Note. * 5 died.

All the 41 symptomatic cases had contact with patients of the previous generation, and 82.9% of them had contact within 1-3 days after the occurrence of hyperthermia in the patients of previous generation (Fig. 4). None of the cases who had contact with SARS patients during the incubation period developed symptoms. Of the 234 asymptomatic contactors, most had contact in the incubation period or in the early stage of SARS (Fig. 5).

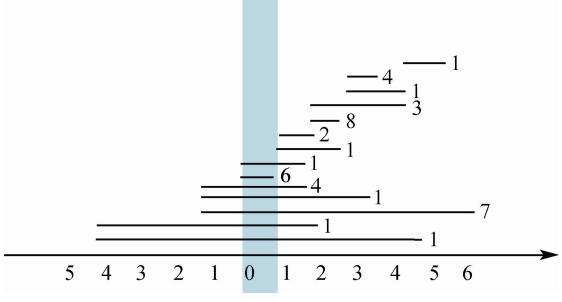

FIG. 4. Simpliflied graph of the periods of contact that the SARS patients contacted the infectors.

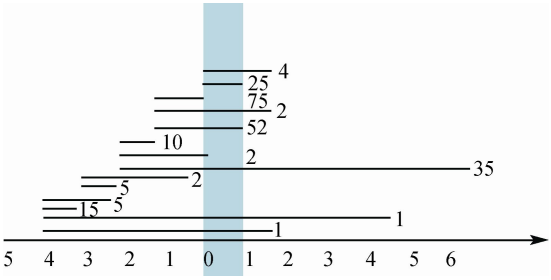

FIG. 5. Simpliflied graph of the periods of contact that the healthy close contactors contacted the infectors.

The ways of contact during the incubation period included working together (11 persons, accounting for 9.6%), living together (25 persons, accounting for 21.9%), and staying in the same classroom (78 persons, accounting for 68.4%). Of those in contact with case A's son and wife, 26 close contactors displayed no symptoms (all faculty members in the same university), and of the 500 individuals including their family members, colleagues, friends and students who had close contact without wearing a mask in the first three days of contact, none progressed to illness.

Ways of contact during the symptomatic period by a secondary infection included by order: nursing care for patients (17/18, accounting for 94.4%), living with patients (2/5, accounting for 40%), visiting patients (14/46, accounting for 30%), performing medical examinations on patients (1/4, accounting for 25%), sharing elevator with patients (7/41, accounting for 17%), and studying in the same classroom with patients (0/47, accounting for 0.0%).

Surveyed Individuals Isolated for Medical Observation

A total of 5 186 persons were isolated in Haidian district of Beijing by May 23, 2003. Of them, 1 028 were surveyed, 24 (2.4%) were SARS cases, and 2 (8.3%) died.

Of the 1 028 surveyed individuals, 630 were isolated for medical observation due to contact with SARS cases, and 398 were isolated for febrile symptoms or close contact with a febrile patient. Of the 630 individuals having contact with SARS cases, 383 (60.8%) developed symptoms, accounting for 37.3% (383/1028) of all the isolated individuals. All the symptomatic cases had contact with SARS patients during the symptomatic period while none of those having contact with SARS patients during the incubation period displayed any illness (Table 4).

TABLE 4

Symptom Development in 630 Close Contactors with SARS in Haidian District, Beijing, 2003

Time of Close Contact	Surveyed Individuals (*n*)	Symptomatic Cases (*n*)	Morbidity Rate (%)
Close Contact with SARS Patients in	383	24	6.3
Close Contact with SARS Patients in	167	0	0
Unknown	50	0	0
No Response	30	0	0
Total	630	24	3.8

TABLE 5

Symptomatic Cases among SARS Contactors in Haidian District (*n*=383)

Ways of Contact	Contactors (*n*)	Symptomatic Cases (*n*)	Morbidity Rate (%)
Providing Nursing Care	61	9	31.1
Visiting Patient	45	4	8.9
Eating Together	122	7	5.7
Sharing Room	90	5	5.6
Sharing Apartment	101	4	4.0
Sharing Floor door or Corridor	85	0	0.0
Sharing Apartment Building	18	0	0.0
Sharing Elevator	75	0	0.0
Sharing Classroom	9	0	0.0

Note. Different ways of contact might duplicate each other, except for sharing a room, an apartment, a floor door, and an apartment building. Only the more relevant ways were calculated.

TABLE 6

Symptom Development among Contactors during the Symptomatic and Incubation Periods in SARS Outbreak in Beijing, 2003

Site	Surveyed Individuals (*n*)	Symptomatic Period			Incubation Period		
		Contactors (*n*)	Symptomatic Cases (*n*)	Attack rate (%)	Contactors (*n*)	Symptomatic Cases (*n*)	Attack Rate (%)
C Transmission Chain	207	125	36	28.8	82	0	0
A Transmission Chain	275	161	41	25.5	114	0	0
Isolated Group	550	383	24	6.3	167	0	0

Note. Fifty persons in the isolated group were unknown for their contact in the symptomatic or incubation period, 30 persons failed to respond to the questions.

None of the 167 individuals having contact with SARS patients in the incubation period developed symptoms. The clinical manifestations varied with the ways of contact in 383 individuals having contact with SARS patients in the symptomatic period. The morbidity rate was 31.1%, which was the highest in those providing nursing case during the symptomatic period (Table 5).

Summary of Results from Three Study Sites

Of the 1 112 persons in close contact with SARS cases who were surveyed at three study sites, 669 had a history of close contact with patients in the symptomatic period. Of these 669 persons, 101 (15.1%) developed symptoms, while of the 363 having close contact during the incubation period, none (0%) did so (Table 6). Of those having contact with SARS patients in the incubation period, none was affected (Table 7).

TABLE 7

Attacks in among Close Contactors during Incubation Period due to Contact during SARS Outbreak in Beijing, 2003

Way of Contact	Surveyed Individuals (*n*)	Attack Cases (*n*)
Living together	134	0
Sharing a Workplace	91	0
Sharing a Classroom	116	0
Providing Nursing Care	4	0
Visiting Patients	7	0
Sharing a Vehicle	4	0
Total	356	0

Note. Different ways of contact might duplicate each other. The ways of contact in some surveyed subjects were unknown.

DISCUSSION

Non-infective SARS in Its Incubation Period

Patients and close contactors in two SARS outbreak transmission chains and individuals isolated for medical observation in a district of Beijing were enrolled in this study. In-depth epidemiological survey and investigation were carried out. We interviewed the patients and their family members more than 10 times to collect specific and reliable information. No individual in contact with SARS patients (including super transmitters) in the incubation period developed symptoms in either of the typical transmission chains. Additionally, clinical manifestations were surveyed in the individuals isolated for medical observation due to the SARS epidemic, and the findings were consistent with those who contacted the patients in the incubation period. There was evidence that all the secondary cases had a history of close contact during the symptomatic period, while of those only having contact with the patients in the incubation period none developed illness, indicating that SARS cases were incapable of transmitting the disease to other human beings during the incubation period. Furthermore, no significant infection was detected in patients by neutralization test and ELISA for SARS-CoV antibody in serum samples from medical workers and family members involved in the treatment of and care for two severe SARS patients (also super transmitters) in the early outbreak stage, indicating that the contactors in the incubation period were not infected either; furthermore, serological tests also confirmed that SARS had no infectivity in the incubation period.

Key Points of the Study in the Incubation Period of SARS

All the scientific papers on SARS published by Chinese experts since 2003 were reviewed. Most of the papers showed that no close contactors in the incubation period of SARS were affected[4-11]. However, they were questioned and could hardly draw a convincing scientific conclusion owing to their small sample size, unavailability of special

laboratory test at early SARS epidemic stage and insufficient data. In contrast, in our survey the data were obtained from two SARS transmission chains and the individuals were isolated from the community, a larger sample size was made possible to overcome the above limitations. Furthermore, the field surveys were executed by the teacher and trainees of Chinese Field Epidemiology Training Program (China-FETP), a professional field epidemiology survey team in China with skills of communication. To complete a survey, as an unique merit they usually had repeated communications with the subject under study. However, our survey also had its limitation due to failure to make laboratory tests accessible to all subjects.

One Chinese scholar believes that SARS can bear infectivity during the incubation period based on many infectious diseases (in particular viral diseases and infectious diseases of the respiratory system) may carry infectivity in their incubation periods and coronavirus is already infectious by the end of the incubation period[12]. However, the findings in our study do not support his conclusion.

Infectivity in the Symptomatic Period

A total of 102 SARS cases were found to have a history of close contact with patients of the previous generation in the symptomatic period in our survey. The potency of infectivity was closely related with the symptoms of patients, ways of contact, environment and duration of contact, and whether precautions were exercised. The most risky ways of contact were: providing emergency treatment or operating the respirator without precautions in a relatively closed setting, accompanying a patient, sharing the same room, followed by sharing the same ward, visiting a patient in hospital, exposure to the secretions of patients and performing routine nursing care, which is consistent with the reported findings[13-14]. Moreover, macro-observation of SARS epidemic found that the highest incidence rate for SARS was seen among the medical workers, accounting for 28.67% of all the cases[15], also failing to support the claim of SARS infectivity during the incubation period (even in the early symptomatic period) because SARS patients would inevitably have close contact with their family members, colleagues and classmates before illness onset or in the early stage. If the patients had infectivity in the incubation period, the infections would have emerged earlier and more frequently among their family members, colleagues and classmates, rather than among medical workers at the highest risk in the epidemic[16-17].

The findings indicate that SARS patients in the symptomatic period are the leading source of infection. The viral load reaches its peak on about day 10 following the emergence of symptoms, and infectivity at this time point may also be the highest[17]. Infectivity of SARS patients is positively correlated with their respiratory tract symptoms. Few patients are infectious when the symptoms appear. They are typically most infectious one week after the onset of symptoms. It is generally believed that patients with severe symptoms carry a stronger infectivity, which is particularly potent when hyperthermia, frequent coughing, and acute respiratory distress syndrome occur[18-19].

No Infectivity of SARS in the Incubation Period and Public Health Decision Making

Individuals in contact with the patients during the incubation period were not ruled out when the close contactors were defined as isolated patients due to an inadequate understanding of SARS infectivity in the early epidemic stage. Based on our findings, isolation of contactors in the incubation period is inappropriate and unnecessary. The findings of the present study were submitted to the Ministry of Health of China in May 2003 and were positively responded. The authors were invited to write certain chapters on Guidelines for Diagnosis and Treatment of Infectious Atypical Pneumonia[20] authorized by the Ministry of Health. According to the Guidelines, close contactors in the symptomatic period should be provided with medical observation, usually family observation, and concentrated medical observation may be placed to prevent cross-infections if necessary. Medical observation is not required for vulnerable individuals having contact with patients in the incubation period.

CONCLUSION

The results of epidemiological surveys of the transmission chains in the two super transmission events and a group of individuals isolated for medical observation in an administrative community indicate that all symptomatic patients have a history of close contact with SARS cases of the previous generation in the symptomatic period, while no close contactors with SARS patients in the incubation period develop symptoms. No significant infection can be detected in close contactors in the incubation period by serological tests. Therefore, it is concluded that SARS cases in the incubation period have no infectivity. Strict management may be unnecessary for individuals in close contact with SARS patients in the incubation period.

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