Original Article

Understanding the Super-spreading Events of SARS in Singapore

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Abstract

Introduction: It has been noted that SARS transmission is characterised by a few super-spreading events (SSEs) giving rise to a disproportionate number of secondary cases. Clinical and environmental features surrounding the index cases involved were compared with cases in non-SSEs. Materials and Methods: Data on 231 cases of probable SARS admitted to Tan Tock Seng Hospital (TTSH) were used. Index cases directly causing 10 or more secondary cases were classified as having been involved in SSEs; all others were defined as non-SSEs. Results: Only 5 cases were involved in SSEs; all 5 were isolated on day 5 of illness or later, and spent at least a brief period in a non-isolation ward; in contrast, amongst the 226 non-SSE cases, only 40.7% and 4.0% were isolated late and admitted to non-isolation wards respectively, and only 3.1% had both these environmental features present; the differences were highly significant ($P = 0.012$, $P < 0.001$ and $P < 0.001$ by Fisher's Exact test). When compared to 7 non-SSE cases with delayed isolation and an admission to non-isolation wards, SSEs were more likely to have co-morbid disease or require ICU care at time of isolation ($P = 0.045$ for both factors). Conclusion: SSEs were likely due to a conglomeration of environmental factors of delayed isolation and admission to a non-isolation ward, coupled with severe disease stage at time of isolation.

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Key words: Communicable diseases, emerging; Cross infection; Disease outbreaks; Infection control

Introduction

Severe acute respiratory syndrome (SARS) was the first emerging infectious disease of this century with true epidemic potential. Worldwide, the virus caused a total of 8098 reported infections and 774 deaths[1] before it was brought under control. In Singapore, the outbreak caused 238 infections from 1 March to 31 May 2003 and resulted in 33 deaths.[2] Since then, there have been several incidents of transmission, both from laboratories[3,4] as well as from the animal reservoir,[5] and a future epidemic remains possible in view of the unknown animal reservoir status.[6]

It has been noted that there is widespread variation in transmission potential amongst cases of SARS. In Singapore, super-spreading events (SSEs) featured strongly in the propagation of the outbreak.[7] SSEs have been observed in community settings with spectacular results, as in the Amoy Gardens incident in Hong Kong;[8] SSEs in community settings were also responsible for cross-border transmission,[9,10] and were likely to have been behind a host of hospital-related outbreaks.[11-15]

In spite of their importance in SARS transmission, it is still unclear how host and environmental factors interact to cause SSEs. In Singapore, it is recognised that at least 5 SSEs occurred.[7] This paper summarises the host and environmental factors surrounding the SSEs, and points out the features common to the events and cases involved. It then compares the circumstances surrounding the SSEs to those surrounding cases not involved in SSEs, in order to test the key hypotheses as to what contributed to the super-spreading phenomenon observed.

Materials and Methods

Data for the analysis were obtained from records of the outbreak of SARS in Singapore from 1 March to 31 May 2003. Case definitions for SARS followed the criteria issued by the World Health Organization,[16] which included

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cases with a clinical diagnosis of probable SARS and cases of suspect SARS with positive virology for SARS Co-V on PCR or serology.

Information on clinical symptoms, and laboratory and radiological investigations, was obtained from a clinical database maintained for patients admitted to Tan Tock Seng Hospital (TTSH) for clinical management of SARS, where 231 of the 238 cases of SARS were managed. Day of illness was counted from onset of symptoms, with the day of onset being Day 1. Day of isolation was defined as the day of illness on which a case was moved into an isolation facility, defined here as a facility where visitors were disallowed and where healthcare staff wore specialised protective equipment while managing patients.

The number of secondary cases generated by each case and the epidemiological links involved were described in the account of the outbreak published elsewhere.[17] Based on this information, source cases with 10 or more secondary cases were classified as having been part of an SSE. The clinical and environmental characteristics of SSEs were then compared against the circumstances surrounding subsets of cases that caused fewer than 10 secondary cases (henceforth referred to as non-SSEs). The choice of 10 or more secondary cases as a cut-off for SSEs was largely arbitrary; one other paper used a similar but smaller figure of 8 or more cases,[11] but we kept to 10 or more for consistency with a previous report on this subject using the Singapore data.[7]

Risk factors considered in the analysis were host factors such as patient demographics, presence of co-morbid disease, as well as chest radiograph abnormalities, clinical signs and symptoms, and indices of disease severity at the

Table 1. Profile of Super-spreading Events

	Super-spreading Event ID				
Factors	**1**	**2**	**3**	**4**	**5**
Age (y)	22	27	53	60	64
Sex	Female	Female	Female	Male	Male
Healthcare worker	No	Yes	No	No	No
Race	Chinese	Filipino	Malay	Chinese	Chinese
Onset date	25-Feb-03	7-Mar-03	12-Mar-03	26-Mar-03	5-Apr-03
Admission date	1-Mar-03	10-Mar-03	†10-Mar-03	†24-Mar-03	8-Apr-03
Date isolated	6-Mar-03	13-Mar-03	20-Mar-03	2-Apr-03	9-Apr-03
Day of illness isolated	D10	D7	D9	D8	D5
Admission to non-isolation ward	TTSH, 6-bed ward	TTSH, 4-bed ward	TTSH, 4-bed ward, then TTSH CCU	SGH, HD ward, then 6-bed ward	NUH, mixed 6- and 8-bed ward
Total duration in non-isolation ward	5 days	3 days	8 days	7 days	<1 day
Co-morbidities	Nil	Nil	Ischaemic heart disease, diabetes mellitus	Ischaemic heart disease, diabetes mellitus, renal impairment	Ischaemic heart disease, diabetes mellitus, liver impairment
Laboratory investigations and chest radiograph					
- positive serology	+	+	Not done	+	Neg. on D5
- positive PCR specimen	+	Not done	Not done	+	+
- earliest abnormal chest radiograph	D5	D7	Prior to onset, from unrelated disease	D9	D4
Symptoms by day of isolation					
- cough	+	-	+	-	+
- dyspnoea	+	-	+	-	+
- vomiting	+	-	-	-	-
- diarrhoea	-	+	+	-	-
Disease course and severity					
- required oxygen by day of isolation	+	-	+	-	+
- ICU or HD care	ICU	-	ICU	HD for bleeding gut	ICU
- intubated by day of isolation	Never ventilated	Never ventilated	Yes	Never ventilated	Yes
- outcome	Discharged	Discharged	Died	Discharged	Died

CCU: coronary care unit; HD: high dependency; ICU: intensive care unit; NUH: National University Hospital; PCR: polymerase chain reaction; SGH: Singapore General Hospital; TTSH: Tan Tock Seng Hospital

† admission prior to onset; for unrelated medical condition

time of isolation. Day of isolation and admission to a non-isolation ward were the environmental factors considered. Admission to a non-isolation ward was defined as being admitted to a healthcare facility without isolation precautions for any period of time. Co-morbid diseases here included those with possible impact on respiratory function (pre-existing ischaemic heart disease/congestive cardiac failure, chronic obstructive pulmonary disease) or those that could depress immune status (diabetes mellitus, malignancies, chronic immunosuppressive therapies). Fisher's Exact tests were used to determine if there was any significant difference between the formation of an SSE and the covariates under consideration.

Results

The clinical features of the 5 cases involved in the super-spreading events have been previously described.[7] Table 1 summarises the case characteristics of the 5 SSEs as well as the environmental circumstances surrounding the cases. The 2 common features are:

- all incidents involved admission, for at least a brief period, to a non-isolation ward, ranging from less than a day in Case 5 to 8 days in case 3
- all 5 index cases were isolated on Day 5 of illness or later

From the database of the remaining 226 cases admitted to TTSH, we found that 92 (40.7%) other cases were isolated on day 5 of illness or later, only 9 (4.0%) were admitted to non-isolation wards, and only 7 (3.1%) had both these environmental features present; the differences were highly significant ($P = 0.012$, $P < 0.001$ and $P < 0.001$ by Fisher's Exact test).

Having established that delayed isolation and admission to non-isolation wards were common to all SSEs, and significantly less common than in non-SSEs, we restricted further comparison of SSEs to the 7 non-SSEs where the cases were also isolated on Day 5 or later, and where admission to a non-isolation ward had occurred (Table 2). We then proceeded to look for differences in the frequencies of the remaining covariates of interest.

In spite of the small number of cases involved, co-morbid disease and illness severity at the time of isolation, as indicated by the need for ICU care, show up as significant risk factors for SSEs. None of the 7 non-SSE cases had a history of co-morbid disease, and none were in the ICU at the time of isolation. However, it must be noted that 2 of the non-SSE cases did progress to require ICU care, and the same 2 cases also eventually succumbed to SARS.

Discussion

This paper identifies the features common to the SSEs in Singapore. The 2 factors common to all the SSEs are a delay to isolation of 5 or more days, and admission to a non-isolation ward, with both factors being far less common in non-SSEs. Our findings that the cases involved in SSEs

Table 2. SSEs vs non-SSEs with Delay to Isolation and Admission to Non-isolation Ward

	SSE cases (n = 5)		Non-SSE cases (n = 7)				
Factors	**n**	**(%)**	**n**	**(%)**	**OR**	**95% CI**	***P* value**
Age ≥35	2	(40.0)	3	(42.9)	2.000	(0.194-20.614)	1.000
Female gender	3	(60.0)	6	(85.7)	0.250	(0.016-3.997)	0.523
Healthcare worker	1	(20.0)	2	(28.6)	0.625	(0.040-9.650)	0.636
Chinese race	3	(60.0)	6	(85.7)	0.250	(0.016-3.997)	0.523
Duration in non-isolation ward ≥3 days	4	(80.0)	2	(28.6)	10.000	(0.648-154.397)	0.242
Co-morbid disease	3	(60.0)	0	(0.0)	-	*NC	0.045
Symptoms present at time of isolation							
- cough	3	(60.0)	6	(85.7)	0.250	(0.016-3.997)	0.523
- shortness of breath	3	(60.0)	2	(28.6)	3.750	(0.331-42.467)	0.558
- vomiting	1	(20.0)	2	(28.6)	0.625	(0.040-9.650)	1.000
- diarrhoea	2	(40.0)	2	(28.6)	1.667	(0.147-18.874)	1.000
CXR changes at time of isolation	4	(80.0)	6	(85.7)	0.667	(0.032-14.033)	1.000
Disease course and severity							
- required oxygen by day of isolation	3	(60.0)	3	(42.9)	2.000	(0.194-20.614)	1.000
- admitted ICU for SARS by day of isolation	3	(60.0)	0	(0.0)	-	*NC	0.045
- intubated by day of isolation	2	(40.0)	0	(0.0)	-	*NC	0.152
- ever required ICU for SARS	3	(60.0)	2	(28.6)	3.750	(0.331-42.467)	0.558
- died of SARS	2	(40.0)	2	(28.6)	1.667	(0.147-18.874)	1.000

95% CI: 95% confidence interval; CXR: chest X-ray; ICU: intensive care unit; OR: odds ratio; SARS: severe acute respiratory syndrome; SSE: super-spreading event

* NC: not calculable, as one cell has 0 observations

were all isolated on Day 5 or later correlates with epidemiologic evidence that suggests a sharp rise of infectivity after Day 5,[18] and a peak of viral positivity by PCR from nasopharyngeal aspirates after Day 6 of illness.[19] However, the strength of the relationship with admission to a non-isolation ward is even greater, and emphasises the nosocomial nature of the disease transmission and the importance of environmental factors in its spread. In fact, in the 7 non-SSEs with delay to isolation and admission to a non-isolation ward, 5 (71%) also had documented transmission, although none of these incidents involved more than 2 secondary cases. In contrast, it has been previously noted that 81% of the Singapore cases did not result in any identifiable secondary case.[7]

However, other than the above 2 environmental factors, our analysis strongly suggests that host factors also play a role in causing the large outbreaks that typify SSEs. When compared to the above 7 non-SSE cases that had similar environmental circumstances, host differences were apparent in spite of the small number of observations available for analysis. The data itself are unable to tell us if the effect is mediated by co-morbid disease or the need for ICU care at the time of isolation, or a combination of both factors. However, others have noted that co-morbid disease is a predictor of poor outcomes, including death and the need for ICU care,[20] and hence lies on the causal pathway for more severe or active disease. Moreover, we emphasise the finding that it is not the ultimate disease outcome that matters, since the main difference is not between the proportion of SSE and non-SSE cases that required ICU, but in the proportion not isolated at the time they were severely ill. We therefore propose that the critical issue is the disease severity at the time the patient was moved to an isolation ward. This implies that, while both environmental and host factors may independently predispose to transmission, it is the conglomeration of the 2 which leads to the greatest amount of transmission. The key ingredient for an SSE appears to be that of a patient who has reached a severe stage of the illness being managed in an unprotected environment.

The above certainly provides a sound context for understanding the other SSEs that have been observed. A review of SARS in healthcare facilities suggested that the peaking of viral load in secretions coinciding with the worsening of symptoms was responsible for the efficient transmission in unprotected healthcare settings.[21] This combination of factors certainly characterised the numerous large outbreaks observed in intensive care and high-dependency units[14,22,23] at other locations. Moreover, key SSEs in the non-healthcare settings, such as the outbreak in hotel M,[9] as well as the flight from Hong Kong to Beijing on which 13 passengers were infected,[10] all involved source patients who succumbed to their illness shortly after, suggesting that they had reached a severe stage in their illness. In addition, our study findings also help to explain the lack of transmission observed in some patients who experienced prolonged delays before diagnosis and isolation[3,24] – as has been postulated by others, these patients may have had a low viral load in their respiratory secretions, and also had less severe clinical disease.[24]

Our study does have its limitations. For one, it relies solely on outbreak investigation records in assigning the number of secondary cases per case. Epidemiological linkages can be biased by pre-suppositions that an SSE had occurred. However, the magnitude of the difference in transmission between SSEs and non-SSEs would suggest that misclassification was unlikely in this case – in all but one instance (where 7 family members were infected), the non-SSEs involved transmission to 3 or fewer secondary cases.[17]

Another issue was the small number of SSEs available for study. The analysis was hence unable to adjust for confounding through a conventional multivariate analysis. In spite of the small numbers, however, it is clear even from the descriptive data that delay in isolation combined with admission to a non-isolation ward were necessary conditions in the Singapore context. In addition, after controlling for potential environmental confounders by restricting our comparison to non-SSEs with the 2 above conditions, there was a difference between the severity of SSE cases and non-SSE cases at time of isolation that was unlikely to be due to chance. However, since 2 of the SSE cases did not have severe respiratory symptoms, it is therefore also likely that disease severity is not the only factor. Additional and as yet unknown host factors may also have been responsible, and remain the subject for further research – possibilities include differences in host response to the virus, and co-infection with other viruses.[25] Moreover, while it is clear that "environmental factors" were associated with a much increased risk of SSEs, we were not able, in this study, to identify if any specific procedures during periods of admission without isolation may have been responsible for the super-spreading events. It has been suggested, for example, that aerosolising procedures may have been responsible,[26] and knowing the exact procedures involved would allow actionable policies to prevent recurrences. It is possible to do a detailed comparison of all procedures done on each of the SARS patients who were admitted to non-isolation wards, and employ the same case-control approach to assess if any of these procedures were associated with the chance of causing an SSE. However, the number of SSEs and non-SSEs who were admitted to non-isolation wards was small – again, a larger collection of cases would be needed to identify any associations while adjusting for

the effects of possible confounders.

However, even without knowing the specific causes behind the SSEs, it was clear from our experience that admission to an unprotected ward environment played a critical role, and detecting and isolating cases early would be the key to preventing occurrences of SSEs.

Conclusion

The Singapore experience strongly suggests that the preconditions for SSEs were delayed isolation and admission to a non-isolation ward. In addition, we found an association between SSEs and disease severity at the time of isolation. Other as yet unknown host factors may also be at work. Also, a larger collection of patients, with more detailed information on the medical interventions performed, would be needed to shed light on the exact procedures that were critical in the generation of SSEs in non-isolation wards. However, regardless of the specific causes, it is clear from our analysis that the key to preventing a recurrence of SSEs would be the early detection and isolation of all SARS cases.

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