

that the quantitative assessment of the effectiveness of public health intervention measures for SARS is a difficult task for modelers. To make models useful for assessing the effects of specific intervention measures and for predicting the future dynamics during an ongoing epidemic, we need improved knowledge on the transmission mechanisms, pathogenesis, and the epidemiologic determinants of the spread of the virus. Any retrospective analysis of the 2003 SARS epidemic that improves our knowledge of SARS epidemiology is welcome.

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Diagnostic Criteria during SARS Outbreak in Hong Kong

To the Editor: A novel coronavirus caused more than 8,000 proba-

ble cases of severe acute respiratory syndrome (SARS) worldwide (1,2) during the 2003 outbreak. Before the etiologic agent was identified, the diagnosis of SARS was made according to a set of clinical-epidemiologic criteria as suggested by the Centers for Disease Control and Prevention (CDC) (1–3). These criteria remained important in the initial diagnosis and prompt isolation of patients because the overall sensitivity of initial reverse transcriptase-polymerase chain reaction (RT-PCR) testing for SARS-associated coronavirus (SARS-CoV) RNA on upper respiratory specimens ranged from approximately 60% to 70% (though sensitivity improved with a second test) (4,5). In a SARS screening clinic at the Prince of Wales emergency department, the positive predictive value (PPV) of these criteria was estimated to be 54% (95% CI 39% to 69%) (6). The relative importance of the clinical versus epidemiologic criteria had not been evaluated. By using paired serologic testing to determine SARS-CoV infection (3), we evaluated the relative importance of the clinical-epidemiologic diagnostic criteria during an outbreak.

Patients with a diagnosis of SARS, and who were admitted to one of five regional hospitals in Hong Kong for isolation and treatment from March 4 to June 6, 2003, were included in this retrospective analysis. Probable SARS case-patients were those who met the CDC clinical criteria for severe respiratory illness of unknown etiology (3), and met the epidemiologic criterion for exposure in either a close or a possible contact. Close contact was defined as caring for, living with, or having direct contact with body fluids of a probable SARS patient (e.g., working in the same medical ward or staying in the same household) within 10 days of initial symptoms. Because Hong Kong was the documented SARS transmission site from February 1 to July 11, 2003,

a modified epidemiologic criterion of possible contact was adopted. Possible contact was defined as staying or working in the same hospital compound, or residing in the same building where case clusters of SARS had been reported, within 10 days of symptoms onset.

Laboratory testing of paired immunoglobulin (Ig) G antibody to SARS-CoV was used to determine infection (7). Positive serologic evidence of infection was defined as a four-fold rise in antibody titer or detection of antibody in convalescent-phase serum. Seronegativity was defined as absence of antibody in convalescent-phase serum obtained ≥ 21 days after symptom onset (3). Seronegativity in this defined time frame (≥ 21 days – serum collected before July 11, 2003, and beyond 28 days) excluded the diagnosis of SARS (3). Samples from patients showing nonspecific fluorescent signals were considered negative for SARS-CoV infection. RT-PCR was performed on clinical specimens (respiratory, fecal) from all patients (1,3–5).

Demographic and laboratory parameters and history of close contact were compared between the seropositive and seronegative groups. Student *t* test was used to analyze continuous variables. A *p* value of <0.05 was considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI) were calculated for categorical variables.

During the study period, 475 patients were hospitalized with probable SARS. One hundred patients were excluded because their serologic results were either missing ($n = 37$) or they died before day 21 of illness (no convalescent-phase serum, $n = 63$). Three hundred seventy-five patients were included in the analyses; 353 (94.1%) patients were serology-positive for SARS-CoV. Two hundred sixty-three of the 353 patients (74.5%) had a 4-fold increase in antibody titers, and 90 of the 353 patients

Table. SARS contact history and demographic and initial laboratory parameters in seropositive and seronegative patients

	Seropositive patients, n = 353 (%)	Seronegative patients, n = 22 (%)	p value or OR (95% CI) ^a
Demographic data			
Age	40.9 ± 17.2	51.2 ± 24.3	0.008
Healthcare workers (HCW)	193 (54.7)	2 (9.1)	12.1 (2.8 to 52.4)
Non-HCW	160 (45.3)	20 (90.9)	
Laboratory parameters on admission			
Total leukocyte count (x 10 ⁹ /L)	6.2 ± 3.2	9.4 ± 7.4	< 0.001
Lymphocyte count (x 10 ⁹ /L)	1.0 ± 0.4	1.2 ± 0.8	0.027
Level of contact			
Definite close contact	322 (91.2)	7 (31.8)	22.3 (8.4 to 58.7)
Possible contact	31 (8.8)	15 (68.2)	
Possible contact plus lymphopenia			
Lymphocyte < 0.8 x 10 ⁹ /L	13 (76.5)	4 (23.5)	
Lymphocyte < 1.0 x 10 ⁹ /L	21 (72.4)	8 (27.6)	
Venue of contact			
Hospital	290 (82.2)	8 (36.4)	8.1 (3.2 to 20.0)
Community	63 (17.8)	14 (63.6)	

^aOR, odds ratio; CI, confidence interval.

(25.5%) had detectable antibody in either acute- or convalescent-phase serum samples (titer 80–5,120). Twenty-two patients (5.9%) had antibody titer <40 in their convalescent-phase serum samples (median = 31 days; range = 21–61 days). No clinical specimens were positive for SARS-CoV by RT-PCR. Thus, the PPV of the clinical-epidemiologic criteria for SARS in our cohort was 0.94 (95% CI 0.91–0.96).

The contact history and demographic and laboratory parameters for both seropositive and seronegative groups are depicted in the Table. The proportion of patients with a history of close contact was significantly higher in the seropositive group than in the seronegative group (91.2% vs 31.8%, OR 22.3; 95% CI 8.4–58.7). Only 8.8% of the patients with serologically confirmed results had no close contact history; 68.2% of the seronegative patients were in this category. The PPV of close contact was 0.98 (95% CI 0.96–0.99), and the PPV of possible contact was 0.67 (95% CI 0.54–0.81). Seropositive patients had a significantly lower lymphocyte

count on admission compared to the seronegative patients (1.0 ± 0.4 vs 1.2 ± 0.8 x 10⁹/L) (p = 0.027). The PPVs for possible contact plus lymphopenia <0.8 x 10⁹/L and <1.0 x 10⁹/L were 0.76 (95% CI 0.56–0.97) and 0.72 (95% CI 0.56–0.89), respectively. Seronegative patients were older (51.2 ± 24.3 vs. 40.9 ± 17.2 years), were less likely to be healthcare workers (90.9% vs. 45.3%), had their venue of contact in the community (63.6% vs. 17.8%), and had a higher total leukocyte count on admission (9.4 ± 7.4 vs. 6.2 ± 3.2 x 10⁹/L). No differences were found in the lactate dehydrogenase, activated partial thromboplastin time, creatinine phosphokinase, and alanine-aminotransferase levels between the two groups.

Fifteen of the 22 seronegative patients responded to antibiotics (8); five died of comorbid illnesses (one of carcinoma of lung, one of metastatic carcinoma of prostate, two of chronic pulmonary diseases, and one of congestive heart failure), and two died of bacterial pneumonia. In four patients, bacterial pathogens were identified (one methicillin-resistant *Staphyl-*

coccus aureus, two *Stenotrophomonas maltophilia*, and one *Pseudomonas aeruginosa*). Also, 15 (68.2%) of the patients had coexisting medical conditions: three had congestive heart failure, four had chronic pulmonary diseases, two had chronic renal failures, two had advanced malignancies, two had diabetes mellitus, and two had Parkinson's disease.

Our findings showed that 5.9% of cases defined as probable SARS on the basis of clinical-epidemiologic criteria had no serologic evidence of coronavirus infection. This set of criteria was associated with a PPV as high as 0.94 in a local outbreak. The PPV of the CDC epidemiologic criterion of close contact was higher (0.98). The PPV of possible contact was 0.67, but when applied with lymphopenia, the PPV became higher. Our analysis illustrated that a history of close contact with patients with SARS-CoV infection is of major importance when diagnosing such infection. This finding supports the hypothesis that SARS-CoV is transmitted through respiratory droplets and physical contact with a patient's body fluids. Although not specific, lymphopenia and its subsequent progress was highly prevalent among SARS patients (8–10). Clinicians are now advised by the World Health Organization that hematologic deviations (e.g., lymphopenia) should be considered in SARS evaluations (1).

Our study was limited by sample size and its retrospective status. Nonetheless, we demonstrated the accuracy of diagnostic criteria in an outbreak and the importance of epidemiologic criteria. Further studies are needed to evaluate the diagnostic accuracy of these criteria in a nonoutbreak situation when the case prevalence is low.

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Malaria Control and Public Health

To the Editor: Malaria continues to cause disease and death in millions of persons living in areas of the world where it is endemic, despite 4 decades of research on vaccines, new drugs, and alternative methods of control. Still, by far the most effective method for reducing and controlling the impact of this disease is indoor residual spraying (IRS) of insecticides. The most cost-effective and safe insecticide has been, and in many instances still is, dichlorodiphenyltrichloroethane (DDT). This intervention is continually under scrutiny, and we address these issues in this letter.

Chen and Rogan (1) claim that DDT causes reduced duration of lactation and increased incidence of preterm births, and they posit that DDT used for malaria control would do as much harm as good. The validity of their arguments requires substantial evidence of a causal relationship between DDT and adverse consequences of DDT IRS for malaria control.

Chen and Rogan dismiss a field study on births and duration of lactation in South African mothers, some of whom occupied houses sprayed with DDT for malaria control (2). However, if claims of large numbers of adverse health effects of DDT IRS are correct, then the study should have detected large differences between DDT-exposed and unexposed populations. According to Chen and Rogan, the median duration of breastfeeding could be as low as 3–4 months when mothers are exposed to high levels of DDT. Thus, a cross-section of breastfeeding infants in the DDT-exposed population should, on average, have been considerably younger than in the unexposed population. In fact, the average age of breastfeeding infants was slightly greater in the DDT-exposed population (8.3 months versus 7.7 months). For both populations,

only an insignificant fraction of mothers could not donate milk. Furthermore, twice the level of dichlorodiphenylethylene (DDE, metabolic breakdown product of DDT) that is claimed to cause reduced duration of lactation in humans has no adverse effect on lactation in rats (3). The authors of the South African study (2) report no difference in rates of stillbirths between the sprayed and unsprayed areas.

The National Institute of Environmental Health Sciences study (4) reported a causal association between DDT and preterm and small-for-gestational-age births but this has not been replicated for African births. The study was not based on a random population of births, and no explanation is offered for including diverse categories of births in the study population.

An earlier study in Sri Lanka presented data on deaths attributed to malaria and to premature births years before DDT was used and years when DDT IRS was used in 21 districts (5). Districts varied greatly in levels of malaria endemicity. After DDT was introduced in 1946, levels of IRS in 21 districts were commensurate with levels of endemic malaria. After 1946, malaria deaths declined greatly and the reduction was greatest where DDT usage was highest. During the same period, deaths attributable to premature births increased slightly. Investigators attributed this to “improvements in reporting and diagnosis rather than any declines in the health of expectant mothers, which on all other criteria showed improvement.” (5). Spearman’s correlation analysis for 21 districts shows that the increase in premature birth deaths was slightly greater in areas with less malaria and DDT use. Thus, the evidence does not support the idea that the reported increase in premature births was a side effect of DDT use. In any case, the increase in deaths attributable to premature births was orders