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Risk-Stratified Seroprevalence of Severe Acute Respiratory Syndrome Coronavirus Among Children in Hong Kong

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ABSTRACT

BACKGROUND. Severe acute respiratory syndrome was relatively mild in children, and the incidence was significantly lower when compared with adults. Although previous seroepidemiological studies demonstrated that asymptomatic infection was uncommon among health care workers and adult contacts of patients with severe acute respiratory syndrome, it is unclear whether this would extend to the pediatric population.

OBJECTIVE. The purpose of this study was to determine the seroprevalence of severe acute respiratory syndrome coronavirus among asymptomatic children living near Amoy Gardens (site of largest community outbreak of severe acute respiratory syndrome in Hong Kong) compared with a low-risk region where no community transmission occurred.

METHODS. The study was conducted from September to October 2003. Target subjects living in the defined high-risk and low-risk areas were approached through the schools within the respective localities. We recruited 353 and 361 children, respectively, from the high-risk and low-risk areas and collected 3 to 5 mL of blood for severe acute respiratory syndrome coronavirus IgG antibody testing by immunofluorescence antibody assay and confirmation by neutralization test. Parents of all of the subjects who joined the study were contacted by telephone, and a standardized questionnaire was administered by a research nurse to collect information including sociodemographic data, history of severe acute respiratory syndrome coronavirus infection in the subjects and members of the household, history of contact with known cases of severe acute respiratory syndrome, presence of severe acute respiratory syndrome-like symptoms since onset of the severe acute respiratory syndrome epidemic, travel history of the child and his/her relatives within the 15 days before any such symptom onset, use of health service as a result of such symptoms, and whether there were deaths of relatives as a result of severe acute respiratory syndrome.

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Key Words
severe acute respiratory syndrome, SARS, SARS-coronavirus seroprevalence, children

Abbreviations
SARS—severe acute respiratory syndrome
AMOY—Amoy Gardens
NTKLOW—Upper and Lower Ngau Tau Kok Estates
WFE—Wah Fu Estate
IgG—immunoglobulin G
IFA—immunofluorescence assay
CI— confidence interval

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RESULTS. Two (0.57%) of 353 asymptomatic children from the high-risk area were tested positive for severe acute respiratory syndrome coronavirus antibody compared with 0 of 361 in the low-risk region. None of the 14 children who lived in the high-risk area and had known contacts with severe acute respiratory syndrome patients were seropositive.

CONCLUSIONS. As in adults, subclinical severe acute respiratory syndrome coronavirus infection was rare in children in the 2003 epidemic. The very low seroprevalence implies little or no population herd immunity to protect against future resurgence of severe acute respiratory syndrome.

THE SEVERE ACUTE respiratory syndrome (SARS) is a newly emerged infectious disease, and its etiology is attributed to a novel coronavirus, SARS coronavirus.[1] Hong Kong was one of the most severely affected areas, with a total of 1755 local residents infected and 302 fatalities.[2] Children, in contrast to adults, had less severe disease, and pediatric SARS constituted only 6.9% of the total number of SARS cases in Hong Kong. The age-specific attack rate was 8.9 cases per 100 000 persons <18 years of age[3] compared with 30.0 cases per 100 000 adults. Similar findings were also observed from a study in Taiwan, where only 7.2% of SARS patients were ≤20 years of age.[4] Reviews on clinical features, investigations, and prognostic indicators on pediatric SARS in Hong Kong have been published[3,5–7]; however, there are a lack of data on possible asymptomatic infection in children at the community level. Because clinical SARS in children was mild, the important question of whether there were more subclinical infections in this age group remains unanswered.

Our objective was to determine the seroprevalence of SARS-coronavirus among asymptomatic children from 3 large housing estates around the Amoy Gardens where a superspreading event occurred giving rise to 330 SARS cases. We compared this with a pediatric sample living in a low-risk housing estate with no reported SARS case in a different district.

METHODS

Study Design

A risk-stratified seroprevalence study of children under 15 years old living in a "high-risk" area (Amoy Gardens [AMOY], Upper and Lower Ngau Tau Kok Estates [NTKLOW], and Telford Gardens) compared with those living in a "low-risk" area (Wah Fu Estate [WFE]).

Definition of High-Risk and Low-Risk Areas

We defined the vicinity of AMOY and NTKLOW as "high-risk areas," because large community outbreaks (330 cases in AMOY of the total 1755 cases over the territory) were documented in these 2 housing estates. This was confirmed by Lai et al,[8] who mapped the Hong Kong SARS outbreak using geographic information system technology, revealing an exceptional spatial clustering of infection in the Kwun Tong district where a heavy concentration of cases were found in these 2 residential areas (Fig 1A). This was the largest single community outbreak of SARS in Hong Kong and worldwide. Wah Fu Estate (WFE), a public housing estate located in Southern Hong Kong Island with similar population density as AMOY and NTKLOW, was chosen as a comparator, because none of its residents were known to be infected with SARS.

Subjects

Target subjects were 6- to 15-year-old primary and junior secondary school children living in AMOY, Ngau Tau Kok Upper and Lower Estates, and Telford Gardens (a housing estate located 100 m from NTKLOW), who were approached through the schools within the locality. Letters explaining the aim of this study were sent to the principals of 9 primary and secondary schools located in the vicinity of AMOY and NTKLOW, and 6 schools agreed to join the study. We identified 901 subjects from the participating schools and distributed consent forms to the students for their parents to sign. We received 372 returns, with a response rate of 40.8%. Of these, 353 children had blood taken for SARS-coronavirus serology (Fig 2).

Target subjects in the low-risk area were those who lived in WFE. Six schools located near WFE were approached, and 5 joined the study. We identified 2860 targets and distributed consent forms. We received 376 (13.1%) returns and collected serum samples from 361 children (Fig 2).

The last known case of SARS in Hong Kong was diagnosed on June 22, 2003. This survey and blood collections were conducted during September and October 2003. The study received ethics approval from the institutional review board of the University of Hong Kong and Hospital Authority, which complies with the Declaration of Helsinki. Written consent was obtained from parents of all of the participating subjects.

Data Collection

A standardized questionnaire collected information including sociodemographic data, history of SARS infection in the subjects and members of the household, history of contact with known cases of SARS, presence of SARS-like symptoms (fever, chills, cough, shortness of breath, headache, generalized weakness, diarrhea, and others) since March 2003, travel history of the child and his/her relatives within the 15 days before any such symptom onset, use of health service as a result of such symptoms, and whether there were deaths of relatives as a result of SARS. Parents of all of the subjects who joined

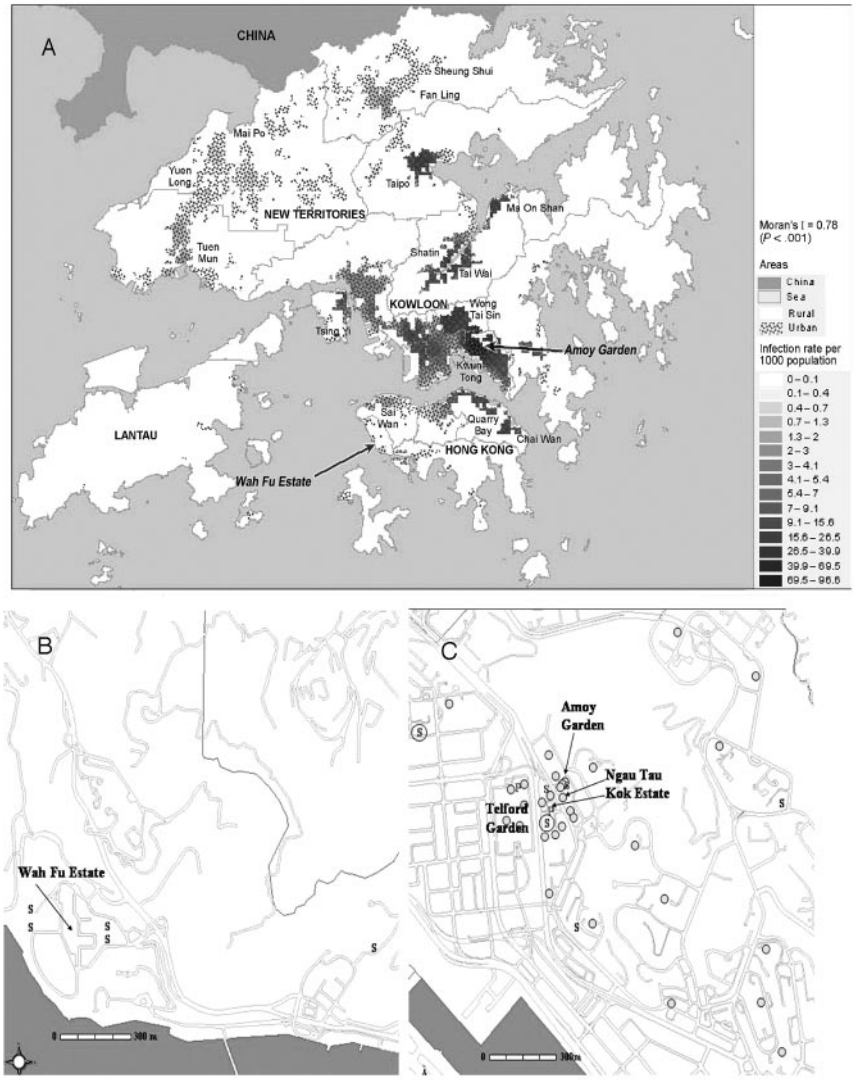

FIGURE 1
A, Map showing the cumulative SARS occurrences in Hong Kong according to geographical distribution from February to June 2004 (Reproduced with permission from Lai PC, Wong CM, Hedley AJ, et al. Understanding the spatial clustering of severe acute respiratory syndrome (SARS) in Hong Kong. *Environ Health Perspect*. 2004;112:1550–1556). B and C, Maps showing the distribution of schools recruited into present study from the low-risk area (WFE) (B) and high-risk area (AMOY area) (C). S indicates locations of schools from which no subject with positive SARS-coronavirus IgG was identified; circled S, locations of schools at which the 2 subjects with positive SARS-coronavirus IgG were studying; P, locations of the buildings in which the 2 subjects with positive SARS-coronavirus IgG were living; ○, locations of buildings where SARS cases were reported.

the study were contacted by telephone, and the above questionnaire was administered by a trained research nurse.

Laboratory Analysis

Three to 5 mL of blood were collected for SARS-coronavirus immunoglobulin G (IgG) antibody testing. All of the serum samples were initially screened by immunofluorescence assay (IFA), and positive results were confirmed by virus neutralization test as recommended by the World Health Organization guidelines on laboratory diagnostic criteria for SARS.[9] For the IFA, microscopic slides coated with SARS-coronavirus (strain 6109)-infected FRhK4 cells were incubated with 10 μL of serum samples at initial dilution of 1:10 for 30 minutes at 37°C. The immunofluorescence titer was taken as the highest dilution that showed positive reaction. Serum samples positive at this screening dilution were retested by using twofold serial dilutions.[10] Previous studies demonstrated that 93% of SARS patients seroconverted by 4 weeks,[11] and 100% seroconverted by 35 days after onset of illness.[12] Also, none of the 2400 healthy blood donor sera were seropositive for SARS-coronavirus when tested by IFA, indicating a specificity of 100%.[13] The antibody level remained constant up to 7 months after infection.[14] Because our subjects had serum samples collected 3 to 4 months after the last reported case of SARS in Hong Kong, we presumed that all past infection would have been detectable, and none would be missed as a result of antibody decline in our test procedures.

Virus neutralization was done on IFA-positive sera in a biosafety level 3 laboratory. The neutralization titer was defined as the highest dilution of serum, which gives 50% cytopathic effect on examination at 72 to 96 hours thereafter. A titer of >10 was considered as positive. A sensitivity of 100% was reported in convalescent-phase serum samples taken a few weeks after the onset of infection in SARS patients.[15]

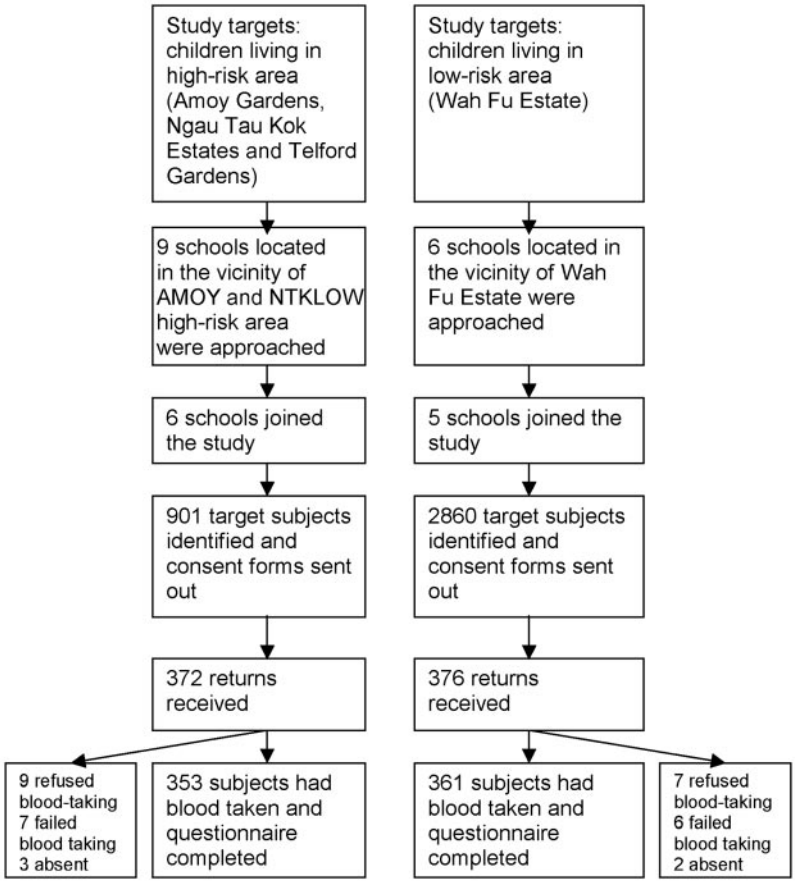

FIGURE 2
Flow diagram showing recruitment of subjects in the high- and low-risk areas.

Statistical Analysis

The χ^2 test with Yates correction was used to compare categorical data, and t test was deployed to compare continuous variables. Binomial 95% confidence intervals (CIs) were generated for the seroprevalence estimates. Fisher's exact test was used to compare seropositivity rates between the high- versus low-risk populations. A $P < .05$ was considered statistically significant. All of the analyses were conducted on SAS 6.12 (SAS Institute, Cary, NC).

RESULTS

Subject characteristics stratified by risk categories are shown in Table 1, and the locations of the studied areas are shown in Fig 1B and C. The SARS-coronavirus infection rate in the high-risk area was >70 per 1000 people, whereas that in the low-risk area was 0.1 to 0.4 per 1000 people. The high-risk area and low-risk area had similar population density; the number of residents below the age of 15 years was 10 340 per km^2 and 9498 per km^2, respectively. The gender ratios of subjects in the 2 groups were similar to those of the children living in the respective areas.[16] None of the subjects in either group reported a previous history of SARS. Two (0.57%) of 353 children (95% CI: 0.07%–2.0%) from the high-risk area were found to be seropositive for SARS-coronavirus antibody. Both had been completely asymptomatic of any SARS-like illness since March 2003 until the test. All 361 children in the low-risk area were seronegative (seroprevalence: 0%; 95% CI: 0%–1.0%). The high-risk versus low-risk areas seropositivity rates were not statistically different ($P = .24$)

The first seropositive case was a 13-year-old boy living in Telford Gardens. His SARS-coronavirus IgG titer was 1:160 by IFA, and the neutralization antibody titer was 1:80. He lived with his parents, elder sister, and grandfather; none of them had any clinical symptoms suggestive of SARS or had traveled away from Hong Kong since the beginning of the SARS epidemic, and their SARS-coronavirus IgG titers were all <1:20 by IFA. The second seropositive case was a 13-year-old girl living in NTKLOW with her parents and her father's friend. Her SARS-coronavirus IgG titer was 1:40 by IFA, and the neutralization antibody titer was 1:40. None of her relatives had clinical symptoms suggestive of SARS or traveled out of Hong Kong, and all of their SARS-coronavirus IgG titers were <1:10 by IFA.

In the high-risk group, 11 (3.1%) children had close family members diagnosed with SARS, including 1 death, whereas none of the family members of children in the control group had SARS ($P = .002$). Three (0.8%) other children had a history of contact with persons who

TABLE 1 **Characteristics of Subjects**

Characteristic	High-Risk Area ($N = 353$)	Low-Risk Area ($N = 361$)	*P*
Gender, *n* (%)			
Male	187 (52.9)	173 (47.9)	.18
Female	166 (47.0)	188 (52.1)	
Age, mean ± SD, y	10.5 ± 2.3	10.5 ± 2.4	.97
Housing type, *n* (%)			
Private housing	132 (37.4)	128 (35.5)	.65
Public housing	221 (62.6)	233 (64.5)	
SARS-coronavirus IgG antibody, *n* (%)			
Positive	2 (0.5)	0 (0)	.24
Any household member infected by SARS, *n* (%)			
Yes	11 (3.1)	0 (0)	.002
No	342 (96.9)	361 (100)	
Any contact with SARS-infected persons outside household, *n* (%)			
Yes	3 (0.8)	0 (0)	.24
No	350 (99.2)	361 (100)	
Any relative(s) died of SARS, *n* (%)			
Yes	1 (0.3)	0 (0)	.99
No	352 (99.7)	361 (100)	
Any following clinical symptoms, *n* (%)			
Yes	43 (12.2)	74 (20.4)	.004
Fever	28 (7.9)	28 (7.8)	1
Chills	17 (4.8)	34 (9.4)	.03
Cough	4 (1.1)	17 (4.7)	.01
Shortness of breath	1 (0.3)	2 (0.6)	1
Headache	4 (1.1)	8 (2.2)	.4
Generalized malaise	5 (1.4)	5 (1.4)	1
Diarrhea	3 (0.8)	5 (1.4)	.75
Any doctor visits because of clinical symptoms			
Yes	40/43 (90.3)	60/74 (81.1)	.14
Still went to school despite having above symptoms			
Yes	10/43 (23.3)	36/74 (48.6)	.01

were diagnosed to have SARS outside the household. All 14 of these children who had known SARS contact were seronegative for SARS-coronavirus. None of the children in the control group had positive contact history.

More children in the low-risk area (20.4%) reported having symptoms during the SARS epidemic compared with the high-risk group (12.2%; $P = .004$). Chills (9.4%) and cough (4.7%) occurred significantly more commonly in children from the low-risk group compared with the high-risk group (4.8% had chills; $P = .03$; and 1.1% had cough; $P = .01$). Overall reported rates of respiratory symptoms were lower in the high-risk group. Most who reported symptoms sought medical attention (93.0% in the high-risk group and 81.1% in the low-risk group; $P = .14$). Despite being unwell, 23.3% in the high-risk group and 48.6% in the low-risk group still went to school.

DISCUSSION

Much progress has been made in characterizing the clinicopathological features and epidemiology of SARS in the past 2 years since its emergence. A review of the clinical features of SARS in adults and children showed that there were 2 major differences between adult and pediatric SARS: (1) the incidence of SARS in children was substantially lower than in adults; and (2) SARS was much milder in children, and none died under the age of 18 years worldwide.[7] The present study is the first community-based seroepidemiological survey in children. The key question concerns whether asymptomatic infection with SARS-coronavirus represented another end of the disease spectrum in children and, if so, whether the potential caseload was significant enough to constitute a source for spread in the community setting.

The fact that pediatric patients affected by SARS had a relatively mild clinical course led some to postulate that children might have only mild symptoms or remain asymptomatic after infected by SARS-coronavirus, might never present to the health care system, and could, thus, explain the lower incidence of SARS in the pediatric population. Our study showed that within a geographic area where superspreading events had occurred, positive serology for SARS-coronavirus in healthy asymptomatic children was also very uncommon (0.57%) and was not statistically different when compared with a low-risk area. Only 2 cases of asymptomatic infection with SARS-coronavirus were documented in our study. "Subclinical" SARS, as revealed by positive anti-SARS-coronavirus IgG in asymptomatic individuals, has been consistently found to be an uncom-

mon entity across different seroepidemiological surveys in both hospital and community settings. A recently published systematic review[17] on SARS-coronavirus seroprevalence studies showed that the overall seroprevalence in asymptomatic population groups was 0.1% (95% CI: 0.02%–0.018%). The seroprevalence in high-risk groups, such as health care workers and close contacts of SARS patients, was only slightly higher (0.23%; 95% CI: 0%–0.37%) when compared with the overall seroprevalence. The study concluded that seroconversion was an extremely rare event in individuals who did not develop SARS, and SARS-coronavirus infection almost certainly led to clinically apparent disease, which, in the majority of patients, was of great severity warranting hospitalization during the 2003 epidemic. In a study on SARS-coronavirus seroprevalence in close contacts of all SARS patients in Hong Kong, only 2 (0.19%) were seropositive, and one of them was a 4-year-old boy who lived with his parents and grandfather, who all had SARS.[15] In fact, when restricted to close contacts of SARS cases from AMOY, the seroprevalence in that study was 1 of 161 (0.62%), which was virtually identical to our present estimate ($P = .99$). Although symptoms of SARS in children were more nonspecific, a majority of patients could be reliably identified by vigilant frontline health care professionals according to stringent diagnostic criteria for case definition.[7] The reported incidence of pediatric SARS from hospital cases very likely represented the true incidence of SARS in Hong Kong children. It was unlikely that subclinical SARS, with such a low prevalence, could have assumed a role in the spread of SARS within the community.

There are several reasons to explain the low incidence of SARS in children from an epidemiologic point of view. The SARS outbreak in Hong Kong first started in the hospital setting involving mostly health care workers and adult patients. There was no reported SARS outbreak in pediatric wards, and it has been routine practice in Hong Kong that children are not allowed to visit hospital wards, thereby limiting their risk of exposure to SARS during that critical period. The transmissibility of SARS in the community setting was low. According to a study on transmission dynamics of SARS-coronavirus in Hong Kong,[18] the basic reproduction number was 2.7 (95% CI: 2.2–3.7), which was much lower when compared with other childhood infectious diseases, such as measles (reproduction number: 7). The inherently low transmissibility of the disease was further reduced by stringent public health measures. As viral shedding progressively increased from onset of illness until approximately day 11 from onset,[9] reduction of onset-to-hospitalization time by rapid isolation of suspected SARS patients limited the spread of the virus before its peak infectivity. Most citizens had heightened awareness of SARS since the 2 major outbreaks, and voluntary reduction in social contacts and quarantine of AMOY Block E residents led to a drop in population contact rates. After the onset of the SARS outbreak and school suspension, many children were kept relatively isolated at home, and together with stringent personal and environmental hygiene measures practiced by the general public, the chance of getting SARS from the community would be minimal. In fact, the majority of SARS patients in Hong Kong, both adults and children, were victims of point-source outbreaks at the Prince of Wales Hospital or AMOY residential complex,[4] with definite history of contact with affected adults in the household or as a result of exposure to a common environmental source. Local epidemiologic studies concluded that SARS-coronavirus had low transmissibility except in close contacts or clinically significant environmental contamination, and infection without a direct epidemiologic link was uncommon.[2] In fact, there was not any spread of SARS in the school setting despite the fact that many infected children had been attending school until they developed symptoms of infection. Retrospectively, the risk of contracting the disease through casual contacts within the community was minimal.

There are several limitations of this study. Selection bias might arise from the relatively low response rate, especially in the low-risk area. Information about those who did not participate in this study was lacking; however, the gender ratio and mean age of the 2 groups of children are similar. Difficulties were encountered when seeking consent from parents, probably because of reluctance toward blood taking in young children, as well as lessening in concern about SARS after the epidemic. Recall and reporting bias about SARS symptoms was also possible, because the time of questionnaire administration was several months after the midst of the SARS epidemic.

CONCLUSIONS

Our study, by determining the prevalence rate of SARS-coronavirus IgG antibody in children in both high-risk and low-risk residential areas, confirmed previous observations that SARS-coronavirus had low transmissibility at the community level, and subclinical SARS-coronavirus infection was rare in children. This community-based serologic survey also supported the idea that SARS-coronavirus was transmitted in very specific settings, and the spread of SARS could be effectively controlled by early detection and isolation of symptomatic patients by means of stringent diagnostic criteria. However, the low seroprevalence rate in the community means that the public will have little protection from herd immunity, should SARS resurge.

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