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Hypothesis

Possible role of an animal vector in the SARS outbreak at Amoy Gardens

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A mass outbreak of severe acute respiratory syndrome (SARS) in the Amoy Gardens housing complex in Hong Kong at the end of March, 2003, affected more than 300 residents in less than a month, and has epidemiologists all over the world puzzled about the mode of transmission of this new disease, which until then was thought to be transmitted solely by respiratory droplets. The source of the outbreak was later traced to an individual with SARS who spent two nights at Amoy Gardens. Official explanations failed to account for the large number of residents infected over a wide area within a short time. A powerful environmental mechanism that efficiently amplified and distributed the causal agent must have been at work to cause this outbreak. One such mechanism could be an animal vector, most probably roof rats, that was infected by the index patient and subsequently spread the disease to more than 150 households.

An outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus^{1,2} arose on 21 March, 2003, among residents of Amoy Gardens, a private housing estate in East Kowloon, Hong Kong. When the outbreak ended in mid-April, a total of 321 residents from 15 blocks had been affected.³

The epidemic had all the features of a common source outbreak, and has been classified by Riley and colleagues as a single "super-spread event".⁴ They also postulated that initial exposure happened on March 19.⁴ Since the mean incubation period of SARS is estimated to be 6.4 days,⁵ and the mean serial interval 8.4 days,⁶ most of the 267 people who fell ill in the first 12 days (March 21 to April 1) must have been primary cases from the same exposure.

This initial exposure was traced to a 33-year-old patient of the Prince of Wales Hospital who had chronic renal disease.³ He lived in Shenzhen and visited his brother in unit 7 on a mid-level floor in Block E of Amoy Gardens on March 14 and 19, and stayed overnight. The index patient developed SARS symptoms on March 14, and had two episodes of mild diarrhoea. SARS virus was subsequently isolated from his blood, urine, and stool. The timing and nature of the epidemic suggest that the outbreak was caused by one but not both of his visits.

There are no communal facilities in Amoy Gardens where a large number of residents can congregate. A common source of food or water contamination has not been identified. Airborne transmission is thought to have been unlikely by the WHO team sent to investigate the outbreak.⁷ How could one person have infected more than 200 others during a single visit?

Prevailing hypotheses

Several hypotheses have been proposed to explain the initial outbreak: (1) contaminated sewage droplets were sucked back into bathrooms by powerful bathroom fans through dried-up floor drains, then escaped through windows and

rose as a plume in a narrow light well (chimney effect); (2) passive carriage by pests; and (3) faecal-oral contact through contaminated surfaces.³

None of these hypotheses can satisfactorily account for the three main puzzles of this outbreak: dose, timing, and spatial distribution. Although we do not know the exact amount of virus needed for clinical disease, to infect more than 200 people with a sole contamination (after dilution of the virus upon leaving the host), the index patient would have needed to excrete a tremendous amount of virus into the environment. A single viral discharge from the index patient has a finite window of infectiousness. Although some research has shown that the SARS virus can live for up to 4 days in diarrhoeal fluid,⁸ on dry surfaces the survival time is estimated to be 24–48 h.⁸ The Amoy Gardens epidemic, therefore, would have required delivery of the virus to more than 200 people within 1–2 days.

Moreover, within block E of the building, floors above the one visited by the index patient were affected more than those below. Households in unit 8 (which had its own separate sewage pipe) were more severely affected than unit 7. Neither observation can be fully accounted for by contaminated sewage. Units hundreds of metres away from the index light well, both upwind and downwind, were affected. The initial cases arose in over 150 apartments in 15 blocks covering thousands of square metres and rising over 100 m into the air.

Static versus dynamic common source

The index patient did not have the mobility nor sufficient dose to serve as a static common source of the epidemic. However, the introduction of an intermediate infected vector as a dynamic common source of infection would provide simultaneously an amplifier and distributor of infectious material. Infected vectors can produce live virus for days, providing the large dose required for the outbreak as well as removing the constraint of survival time of the virus. The most likely vector at Amoy Gardens is the roof rat (black rat, *Rattus rattus*).

The rat vector hypothesis

I suggest that the epidemic could have been started on March 14 by a rat from block E going into the apartment visited by the index patient and being infected by contaminated material, such as used tissue paper, leftover food, or excreta. The incubation period in rats infected by

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naturally occurring coronavirus such as the sialodacryoadenitis virus is short (2–5 days), thus the first infected rat would have become contagious around March 19. Naturally occurring coronavirus disease is benign, lasting about 7 days, and there is no carrier state.⁹ Secretions from infected rats, such as urine, droppings, or saliva, contain large amounts of virus and are highly contagious.⁹ Roof rats prefer to forage for food above ground in elevated areas.¹⁰ They are also territorial and habitual, and tend to follow the same pathways between their nest and food sources and make return visits time after time.¹¹ Their range of activity when looking for food is about 30–45 m.¹¹ The lightwell between units 7 and 8 of block E is very narrow (1.5 m) with two separate sewage pipes running vertically along the walls close to the bathroom windows. Clothes-lines are installed outside the bathrooms of each unit, and these almost touch one another, providing convenient bridges for rats to travel up and down the building. The first infected rats would probably have been used to visiting the middle and upper floors of units 7 and 8 in block E, and subsequently made many returns to these units, accounting for the unusual concentration of cases on these floors. Roof rats seldom go to the bottom of a building to look for food, thus the lower floors were spared.

The infection could have been passed from rat to man either by rats entering households and leaving infectious material in bathrooms and kitchens, or by contamination of clothing on clothes-lines. The first infected rats could also have spread the virus to other rats in block E and in other blocks, starting an epidemic among rats, and providing the common source for the epidemic in people. That rats further away from block E were less likely to be infected would account for the fact that the epidemic was earliest and most intense in the blocks closest to block E.³ The epidemic started to decline on April 1, 2003, when residents in block E were evacuated, when rats would have recovered from their infection, and when extensive rat trapping and baiting started at Amoy Gardens. However, the epidemic did not end for another 2 weeks, with 54 more cases.

Circumstantial evidence for the existence of a rat vector

Several pieces of circumstantial evidence lend support to the theory of a rat vector. First, virologists strongly suspect that the SARS coronavirus originated from animals and jumped species to infect man. A virus virtually identical to the SARS coronavirus was isolated in Shenzhen, China, from six masked palm civets and a raccoon dog.¹² Antibodies to this virus were also found in the blood of a badger.¹² Thus, the SARS virus can probably survive and infect animals as well as humans.

Second, viral remnants have been detected in four of eight samples of rat droppings found around Amoy Gardens and in the throat or rectal swabs of five housecats, one dog, and at least one rat from the estate.¹³ One of the cats also tested positive for antibodies to the SARS virus.¹³

Third, Amoy Gardens is located in one of the most densely populated areas in Hong Kong, known for poor hygiene and rat infestation.¹⁴ If rat infestation is common, an epidemic in rats can easily cause an epidemic in humans.

Fourth, rats are territorial, mobile, and can reach high floors through external pipes. The sewage and water pipes at Amoy Gardens are located very close to bathroom windows and allow rats easy access into households.

Fifth, viral footprints were found around toilet bowls,

kitchen sinks, and on kitchen floors in several households in block E, but not in bedrooms¹⁴—an unlikely pattern if contamination was caused by man. In other smaller outbreaks elsewhere in Hong Kong, remnants of SARS virus were detected on the surface of a pipe on the roof of an affected building¹⁵ and on the window sill of an unaffected neighbour of a household affected by SARS;¹⁶ both places are unlikely to have been contaminated by people.

Sixth, presenting symptoms and clinical course of patients from Amoy Gardens differed substantially from those of other SARS patients, with more diarrhoea, more admissions to intensive care units, and higher mortality,¹⁷ suggesting a different route of infection, substantial mutation of the virus, or both.

Lastly, coronaviruses are RNA viruses with a great ability to reshuffle genes. The SARS virus has already shown genome sequence differences in different reports.^{18,19} Haijema and co-workers²⁰ successfully incorporated the coat protein gene from a mouse coronavirus into a feline coronavirus (feline infectious peritonitis virus, FIPV) by injecting cat cells with FIPV and adding a gene fragment from a mouse coronavirus. The exchange of the feline coat gene and the mouse coat gene took only several hours and made the new FIPV infectious to mouse cells. If rats at Amoy Gardens had naturally occurring rat coronavirus and were exposed simultaneously to the SARS virus, gene reshuffling might have produced a new SARS virus that was transmissible to both rats and humans.

Weaknesses of the rat vector hypothesis

This theory also has some weaknesses. So far no rodent model for SARS has been established. Autopsies done on four rats caught around Amoy found no signs of active disease.⁷ However, as suggested by Haijema and colleagues, the simultaneous presence of another rat coronavirus might be necessary to successfully infect rats with SARS. Rats might also be able to transmit SARS without overt disease.

Although virus was found in rat droppings, this contamination could have been caused passively. Furthermore, the mode of transmission of the virus from man to rat and back to man is not clear. Finally, to start an epidemic affecting so many residents, many rats would have to be infected within a short period of time, and infectiousness among rats would have to be short-lived for the epidemic to die out eventually.

Future work

The rat vector hypothesis is a strong possibility that needs to be further explored. Epidemiological case-control studies could be undertaken to identify behavioural risk factors and possible mechanisms for rat-to-man infections. For example, if rat contamination occurs at night, people using kitchen and bathroom facilities early in the morning, when cooking breakfast, taking showers, and so on, will be at increased risk. Housewives will be affected more than husbands working away from home. Small children who crawl on the floor will also be at higher risk.

Detailed comparisons of incubation period, presenting symptoms, clinical course, and outcome can be done between patients from Amoy Gardens and other patients with SARS. The existence of several distinct types of SARS should be explored. Viral studies of Amoy isolates should be done to ascertain whether they have undergone substantial mutation when compared with isolates from other patients. Viral genomes from different series of patients should be compared.

To seek evidence of viral infection in the proposed vector, rats and droppings should be sampled from all the blocks in Amoy Gardens. Investigations of rat populations (if any) in the many blocks that were completely unaffected by SARS might provide clues. Rats in neighbourhoods around Amoy Gardens and elsewhere, where clusters of cases have occurred, should also be studied. Droppings should be assayed for viral presence by culture and PCR. Rats should be thoroughly autopsied to study for pathological changes and to determine the distribution of virus and viral gene products in tissues, urine, saliva, and faeces. Serological studies should be done to detect antibodies.

Infection of rats could be investigated experimentally by exposure to SARS virus by inhalation, ingestion, and injection, in rats of different ages, and in pregnant rats to assess intrauterine infection. After exposure, disease occurrence, antibody formation, ability to pass virus to the environment, and development of tolerance and carrier state could be investigated.

Conflict of interest statement
None declared.

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