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EDITORIAL COMMENTARY

The Cat's in the Bag: Despite Limited Cat-to-Cat Severe Acute Respiratory Syndrome Coronavirus 2 Transmission, One Health Surveillance Efforts Are Needed

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(See the Major Article by Bao et al, on pages 1313–21.)

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At the 1-year anniversary of the coronavirus disease 2019 (COVID-19) pandemic, we are living through one of the largest health events of the century, where >109 million people have become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and >2.4 million have died [1]. Remarkably, SARS-CoV-2, a zoonotic virus of likely bat origin, infrequently has caused illnesses and deaths among domestic animal populations (except mink). In the United States alone, >27 million people have had confirmed COVID-19, yet only 132 animals (of 3625 tested) were diagnosed as positive for SARS-CoV-2 infection as of 15 January 2021. Notably, the animal infections were primarily domestic (n = 58 [44%]) or exotic (n = 14 [11%]) cats, including tigers, lions, snow leopards, and a cougar [1–3]. Taken together, the high SARS-CoV-2 infectivity rate among the human population, the significant COVID-19 case numbers in community settings, and the commonality of pet ownership, the low rates of infection within the domestic cat population are reassuring and may suggest that cats have resistance to symptomatic SARS-CoV-2 infection. However, due to gaps in One Health surveillance infrastructures focused on zoonotic pathogens, and in some cases guidance against routine testing in animals because of limited resources [4, 5], the low case counts among domestic cats may be the tip of the iceberg. Most testing of domestic and exotic animals has been ad hoc, and little is known about the potential for non-human species to serve as transient or longer-term reservoirs for SARS-CoV-2, particularly within the 2 most implicated animal families: mustelids (mink) and felids (cats).

Susceptibility of domestic and exotic felids to SARS-CoV-2 has been established via experimental infection under laboratory conditions [6, 7] and natural infection in community and zoological collection settings [2, 8–10]. The report by Bao et al in this issue of *The Journal of Infectious Diseases* builds on prior experimental studies of domestic cats that established the potential for cat-to-cat transmission [11, 12] to describe attenuation in virus transmissibility through serial passage in both male and female cohoused cats. In other words, the authors addressed the question of high epidemiological relevance: After a series of cat-to-cat transmission events, does the infectivity of SARS-CoV-2 in the subsequently infected cats weaken? To answer this question, researchers assessed serial passage between infected (ie, donor) cats and naive recipient cats. Donor and naive cats had 2 days of direct contact which began 1 day after donor cat inoculation. They repeated this chain for a second and third passage and assessed whether the original donor cats could transmit to new naive cats at a later point, modeling a late-stage exposure (6–8 days postinfection). Recipient cats demonstrated lower viral shedding rates compared to the donor cats for both early- and late-stage exposures. Furthermore, transmissibility decreased during late-stage exposure compared to early-stage. The authors did not detect any genetic changes in the first passage of virus; however, live virus could not be recovered from subsequent passages, which precluded genomic analysis. Of note, antibody titers at 14 days postinfection were approximately 8-fold lower for first-passage recipient cats than donor cats and were below the limit of detection for recipient cats in the second or later passages.

Using young adult cats (8–18 months), Bao et al confirmed prior pathological and clinical findings [6, 7, 11]: chiefly,

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that infection in young cats appears to be largely subclinical, with few overt signs and mild pathological changes in lung and intestinal tissues. Pathological findings coincided with co-localization of SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors, the functional mediator for SARS-CoV-2 infection [13]. Finally, they conducted ACE phylogenetic analysis compared to other susceptible species, and projected weaker interactions for feline ACE2 compared to human receptors, which is one potential mechanism to explain their findings of reduced transmissibility.

These data convey important implications for natural infections in community settings, where there have been some concerns for the potential for domestic and feral cat populations to serve as reservoirs for human exposure [11, 12]. Good news first: It seems likely that sustained cat-to-cat transmission (eg, in feral cat colonies) will be limited for the tested strain. Nonetheless, the results from Bao et al reinforce evidence that susceptible cats can become infected given exposure to an infected cat at both earlier and later stages of donor cat infection and support recommendations that humans with suspected or diagnosed COVID-19 should practice contact precautions when handling their family cats to prevent potential human-cat-human transmission (or a rare-but-possible scenario of human-cat-cat-human transmission). Another result reinforced by these data and the previous reports is the uncertain duration of antibody-mediated immunity among cats. Bao et al identified that cats in the later passages neither shed virus nor seroconverted. While this is encouraging for concerns related to sustained transmission, it does suggest that these tertiary infected cats would remain susceptible. Furthermore, at least 1 prior study [14] suggested that a short duration of immunity in domestic cats could occur due to the brief peak in neutralizing antibodies and a reduction in natural titer concentrations. To date, all studies of naturally infected cats have been limited by small sample size, and laboratory studies have targeted young, healthy adult cats. This suggests that larger studies with greater population variance are needed to better understand the natural course of infection and immunity in community populations of cats, including older cats and those with comorbidities. Such studies would allow surveillance for more rare events of public health and veterinary importance, such as longer-term virus shedding and more severe clinical disease and pathology. Given that rates of more severe disease are 10%–15% in humans overall—and much lower among adolescents and young adults [15]—similar or lower rates in felines would require studies that evaluated hundreds or thousands of exposed cats.

Another reassuring element of this study—at least in the highly controlled conditions of cat-to-cat passage in a laboratory setting—was that the authors found genetic stability of the SARS-CoV-2 strain used in the cats. This is in contrast to identification of a mink-associated variant in Denmark with spread into people, including those not in contact with mink [16], where mutations in this strain occurred in the spike protein, the leading vaccine target. Spike protein mutations have already occurred in the B.1.135 variant from South Africa, which may increase penetrance in vaccinated individuals and reduce antibody treatment effectiveness [17]. The mink-associated variant also showed increased binding to the mink ACE2 receptor, suggesting potential host adaptation [18]. Investigators also evaluated 24 stray cats on infected mink farms in the Netherlands and identified that 7 (29%) developed SARS-CoV-2 antibodies (suggesting exposure), and 1 was weakly positive by polymerase chain reaction [19]. Unfortunately, live virus could not be recovered from this cat, precluding genomic analysis [19]. If a variant with improved binding to the cat ACE2 receptor should emerge, it is possible that this would impact cat-to-cat transmission and increase the potential for cats to serve as reservoirs of the virus.

Despite recent attention to the need for outbreak response and preparedness efforts focused at the human-animal interface [20–24], necessary resources have been limited for epidemiological surveillance in cats and other domestic animals for COVID-19 or genomic surveillance for SARS-CoV-2 variants from these species [25]. As of mid-February 2021, the United States Centers for Disease Control and Prevention does not recommend routine testing of privately owned domestic cats in contact with people confirmed with COVID-19 unless the cat also shows clinical signs consistent with SARS-CoV-2 infection [5]. Improved One Health approaches—targeting humans, animals, and the environment—to extend research-based and surveillance testing of felids in community, veterinary hospital, and zoological collection settings are warranted and should be a public health priority. The importance of One Health surveillance systems extends beyond this pandemic [25]. Given that up to 75% of emerging infectious diseases are zoonotic in origin [26, 27], a comprehensive and global One Health surveillance system is needed to guard against pathogens with higher spillover propensity and strengthen global health security. This may require a system-wide approach that engages collaboration at the policy, institutional, and operational levels [28]. Denmark's antimicrobial-resistant pathogen surveillance system [29] is one example of the kind of integrated approach needed to bolster preparedness and inform response mechanisms for all zoonotic diseases, including a future "Disease X" [30].

In a scientific landscape with so many uncertainties, we also should recognize the essential companionship roles that domestic cats and other pets provide to people, particularly those otherwise isolated by COVID-19 pandemic restrictions. Equally, exotic felids in the wild serve critical ecological niches, and in captive settings, aid in important education and conservation efforts. Despite the important findings by Bao et al that

extended cat-to-cat transmission chains with the current SARS-CoV-2 variant are unlikely, their data nonetheless support the susceptibility of felids to the virus and highlight the potential for cat-to-cat transmission, particularly at certain stages of the donor cat's infection. As the global struggle to contain the COVID-19 pandemic continues, scientists and political bodies should continue to recognize the importance of SARS-CoV-2 transmission dynamics in animal populations and investigate to prevent potential genetic drift and spillover into the human population. Ongoing and future One Health responses will need to balance these surveillance and other health security activities with attention to the importance of the human-animal bond.

Notes

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