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Backward transmission of COVID-19 from humans to animals may propagate reinfections and induce vaccine failure

Shanshan He¹ · Jie Han¹ · Eric Lichtfouse²,³

Virus-carrying animal hosts

The coronavirus disease 2019 (COVID-19) pandemic is becoming the greatest public health crisis since the influenza pandemic in 1918 (Sanders et al. 2020). Indeed, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread to 219 countries and regions, causing over 46.5 million human infections including more than 1.2 million deaths as of November 3, 2020 (WHO 2020). So far, research has focused on its transmission from animals to humans—‘zoonosis’—to explain its spillover to humans, yet its further transmission from humans to animals—‘anthroponosis’ or ‘reverse zoonosis’—has been much less considered. Knowledge concerning the relationships between its human and animal hosts is still limited, and a consensus has yet to be reached on the animal origin of COVID-19. It is known that SARS-CoV-2 shares 79.6% of its genome sequences with SARS-CoV-1, a strain that has infected humans, bats and palm civets in 2003. Also, SARS-CoV-2 shares 96.2% of its sequences with a bat coronavirus isolated from Rhinolophus affinis, suggesting that bats may be the natural hosts of SARS-CoV-2 (Lu et al. 2020; Paraskevis et al. 2020; Zhou et al. 2020). Cats, ferrets, minks, pangolins, snakes and turtles have been postulated as intermediate hosts of the novel coronavirus (Ji et al. 2020; Li et al. 2020; Nabi et al. 2020; Wu et al. 2020). Here we show that COVID-19 transmission from humans to animals is likely to amplify mutations and, in turn, to re-infect humans with deadlier mutants.

Infectable vertebrates

The infection of SARS-CoV-2 is induced by interactions between the SARS-CoV-2 receptor-binding domain and angiotensin-converting enzyme 2 (ACE2) receptor proteins (Santini and Edwards 2020; Wu et al. 2020; Zhou et al. 2020). As a consequence, a diverse range of vertebrates can be potentially infected by SARS-CoV-2 via their ACE2 receptors. This assumption is supported by the findings of ACE2 receptors in over 400 vertebrate species including both domestic and wild animals (Damas et al. 2020; Wu et al. 2020. SARS-CoV-2 infections have been recently confirmed in mammals including cats, monkeys, ferrets and hamsters (Santini and Edwards 2020). Studies have also shown that infected cats, ferrets and hamsters were capable of spreading SARS-CoV-2 to other animals in laboratory settings (Kim et al. 2020; Shi et al. 2020; Sia et al. 2020). Overall, contamination and cross-infection of vertebrate species are likely.

Transmission via human-animal contact

About 70% of emerging infectious diseases and almost all recent pandemics caused by zoonoses are correlated with aggressive land reclamation, intensified livestock production, increased wildlife hunting and trading activities by humans (Di Marco et al. 2020). Conversely, regular or inadvertent interactions between infected persons and wild or domestic animals allow COVID-19 to be transmitted in the reverse direction. Anthroponosis is more likely to occur in areas with high prevalence of human infection and co-existing wild habitants, e.g., in city suburbs. This hypothesis is supported by recent incidents and studies. For instance,
domestic cats and dogs owned by infected individuals have been tested positive for SARS-CoV-2, some showing no specific symptoms (Santini and Edwards 2020; Sit et al. 2020). Following an incident at the Bronx Zoo in New York City, direct human-to-animal transmission has been proposed from the epidemiological data and genetic similarities of SARS-CoV-2 strains isolated from tigers and their keepers (McAloose et al. 2020). Minks infected with SARS-CoV-2 have also been identified on farms in the Netherlands, Denmark, Spain and the USA, where infected farm workers were speculated as sources of infection (CDC 2020; Oreshkova et al. 2020). Human infection acquired from infected minks, i.e., reverse anthroponosis, was also suspected on two mink farms in the Netherlands reporting human-to-mink transmission (Oreshkova et al. 2020). Converging evidence thus points to possible underestimated transmission from humans to animals and further spillover back to humans.

**Anthropogenic wastes as secondary routes**

Apart from direct human-to-animal transmission, e.g., by physical contact with domestic and wild animals, transmission to animals via human wastes is also likely. Potentially, animals may come into contact with wastes from infected households that contain infectious human biological matter, e.g., nasal discharge, phlegm, saliva, semen, vaginal fluids, blood, urine and feces (Franklin and Bevins 2020; Han and He 2020; Nabi et al. 2020). The main route is probably water contamination due to the enteric propagation of the virus. Also, improper disposal of contaminated personal protective equipment constitutes a source of COVID-19 infection for wild and stray animals (Fadare and Okoffo 2020; Kalina and Tilley 2020). Particularly, masks, face coverings, gloves, tissues and wipes are routinely used in response to the current pandemic, creating enormous amounts of single-use items that could be potentially infected with the virus (UNEP 2020). When not managed timely and soundly, these are subject to open dumping, which pose risks of infection for domestic and wild animals in surrounding environments. This is supported by the fact that SARS-CoV-2 could survive for several days on face masks, tissues, and other household materials under common conditions (Chin et al. 2020; Han et al. 2020; van Doremalen et al. 2020). In addition, water contamination is possible due to the enteric propagation of the virus and substantial viral loadings found in human excreta, especially in communities with unimproved sanitary facilities or recurring combined sewage overflows (Han and He 2020; Sun and Han 2020).

**Mutations and gene mayonnaise of SARS-CoV-2**

The genetic diversity of coronaviruses is caused by accumulation of mutations and high-frequency homologous recombination, which favor tissue tropism, breaking of interspecies barriers and adapting to ecological variations (Amer 2018). There is also a form of template switching similar to homologous recombination, although the mechanism is different. The in-host genetic diversity and host-switching events could incite the virus to adapt to a wider array of selective pressures, ultimately inducing different diseases and symptoms in hosts (Borucki et al. 2013).

Members of the coronaviridae family, e.g., SARS and the Middle East respiratory syndrome (MERS)-related coronavirus, have been shown to cross the interspecies barrier (Amer 2018). Graham and Baric (2010) found that the recombination of SARS in the spike glycoprotein genes might have mediated the initial cross-species transmission event from bats to other mammals. Moreover, Ji et al. (2020) pointed out that a homologous recombination of SARS-CoV-2 may occur between a bat coronavirus and a coronavirus of an unknown origin within the viral spike glycoprotein gene. This study found that SARS-CoV-2 has highly similar genetic information with bat coronavirus. Lau et al. (2020) further showed that the entire genome of SARS-CoV-2 is most closely related to the SARSr-Ra-BatCoV RaTG13 from an intermediate horseshoe bat, except for its receptor-binding domain which is closest to pangolin-SARSr-CoVs, suggesting that SARS-CoV-2 is a recombinant virus. Overall, these findings indicate the complex origin of SARS-CoV-2, where evolutionary recombination and strong purifying selection occurred between strains from distinct host species before it spilled over to humans (Li et al. 2020; Wu et al. 2020; Sallard et al. 2020). The back-and-forth transmission between human and wild species, when it occurs, may further enhance the genetic diversity of the virus.

**Lessons from flu vaccines**

Reverse zoonosis of SARS-CoV-2 may seed unrestrained spread and mutations in infectable wild species and, perhaps at some stage, transmission of novel strains back to humans. Without human intervention, the dense roosting behavior and long foraging range of some wild species may facilitate exchange of viruses and recombination. Lau et al. (2010) found that recombination events occurred between strains of Rousettus bat coronavirus Ro-BatCoV HKU9 from different bat individuals, which might have allowed the same bat to be infected by at least two distinct genotypes. Likewise, different species coinfectected with influenza A
genotypes potentially facilitated genetic reassortment of the virus, for instance, between human and avian virus strains. These activities can create new genotypes with substantial antigenic changes that can result in an influenza pandemic and produce a virulent strain (Carrat et al. 2007). It should be noted that genetic recombination is a known contributor to major shifts in influenza antigenicity. As a consequence, the influenza season vaccine becomes less effective due to genetic shift by mutations of the virus with time (Carrat et al. 2007).

A meta-analysis of data in 30 selected publications showed that, between 2010–2011 and 2014–2015, the pooled seasonal influenza vaccine effectiveness was 51% for any influenza among people aged 18–64 and 37% among those 65 and older (Rondy et al. 2020). Notably, the study found that vaccine effectiveness against influenza A (H3N2) was 43% among persons aged ≥ 65 in seasons when circulating and vaccine strains were antigenically similar, but only 14% in seasons when variant viruses of influenza A (H3N2) predominated (Rondy et al. 2020). In contrast, the effectiveness of human vaccines against bacterial pathogens is generally much higher, given the low mutation rates of the latter. In a study enrolling 782 cases and 2,512 controls, Whitney et al (2006) found that the effectiveness of seven-valent pneumococcal conjugate vaccine (PCV-7) for bacteraemic pneumonia was 98% in healthy children. We hypothesize that similar risks may exist in the current and future development of vaccines against the novel coronavirus. Once SARS-CoV-2 spills from human to wildlife, the spontaneous behaviors of wild species such as foraging, predation, mating and defecating enable both in-species and cross-species transmission, facilitating genotype changes and evolution of SARS-CoV-2 in various wildlife reservoirs. Mutated viruses may then spillover to humans again through different natural or intermediate hosts, forming a dangerous loop of zoonosis, anthroponosis and reverse anthroponosis of an evolving virus between human and animal hosts. Once transmitted to humans, those novel strains will pose significant challenges for infection control by causing reinfections, re-emergent outbreaks and rendering current vaccines less effective.

Deadly reinfection

It is commonly accepted that, once already infected then cured, an individual is better protected against the infectious agent, yet this might not be true in some cases of rapidly mutating viruses such as COVID-19. At least seven cases of SARS-CoV-2 reinfections have been reported since the first case was reported in Hong Kong on August 24,
2020 (Larson et al. 2020; Mulder et al. 2020; Prado-Viviat et al. 2020; Tillett et al. 2020; To et al. 2020; Torres et al. 2020; Van Elslande et al. 2020). Remarkably, in four cases, patients showed more severe symptoms than previous symptoms from their first infection, including one severe case where the individual died shortly after the reinfection. In all seven cases, viral strains isolated from the reinfected individuals showed substantial genetic differences from the initial strains causing their first infection. Less severe secondary infections have also been reported. The emerging cases of SARS-CoV-2 reinfections are likely to be caused by mutations and continuing evolution of the novel coronavirus. There are risks that novel strains of SARS-CoV-2 may emerge in wildlife reservoirs by accumulating point mutations and homologous recombination as it spreads in an uncontrolled manner between different hosts and species. Reverse anthroponosis of novel strains, once it occurs, may render current COVID-19 vaccines less effective (Dai et al. 2020). The virus may spill back and forth between humans and animals, thus forming a vicious loop with prolonged transmission diversity in adaptation of Bovine Coronavirus to new host environments. PLoS ONE 8(1):e52752. https://doi.org/10.1371/journal.pone.0052752

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Conflict of interest  The authors declare that they have no conflict of interest.

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Compliance with ethical standards

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