Research in Veterinary Science 131 (2020) 21–23

Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

COVID-19 from veterinary medicine and one health perspectives: What animal coronaviruses have taught us

Nicola Decaro[a], Vito Martella[a,*], Linda J. Saif[b,c], Canio Buonavoglia[a]

[a] Department of Veterinary Medicine, University of Bari Aldo Moro, Strada Prov. per Casamassima Km 3, 70010 Valenzano (BA), Italy
[b] Viruses and Emerging Pathogens Program, Infectious Diseases Institute, The Ohio State University, Columbus, 1680 Madison Ave, Wooster, OH 44691, USA
[c] Food Animal Health Research Program, Ohio Agricultural Research and Development Center, CFAES, Department of Veterinary Preventive Medicine, The Ohio State, 1680 Madison Ave, Wooster, OH 44691, USA

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Veterinary medicine
Animal coronaviruses
One health

1. Introduction

Coronaviruses (CoVs) are enveloped, single-stranded, positive-sense RNA viruses displaying an exceptional genetic plasticity driven by accumulation of point mutations and recombination events. This genetic variation is responsible for continuous emergence of viral strains with increased virulence, different tissue tropism and/or expanded host range (Buonavoglia et al., 2006). CoVs are currently classified within four genera, *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*, that recognise bats, birds and likely rodents as natural reservoirs.

In December 2019, cases of undiagnosed pneumonia started being reported in Wuhan, Hubei, China. On January 9 2020, the Chinese authorities indicated that a novel CoV was associated with the severe respiratory disease. The first patient with unexplained pneumonia, identified in December 8 2019, came from Wuhan South China Seafood Market. Initially, other patients were linked to the same seafood and live animal market, suggesting an animal origin for the initial spread to humans. Subsequent investigations revealed that the crowded seafood market only boosted circulation of the novel CoV and spread it to the whole city in early December 2019, whereas based on the genome data the virus likely began spreading from person to person in early December or even as early as late November. The first documented human case has been dated back to November 17 2019.

The novel human CoV (HCoV) is a betacoronavirus genetically related to Severe acute respiratory syndrome (SARS) CoV and only distantly related to Middle East respiratory syndrome CoV (MERS-CoV) and it was designated as SARS type 2 CoV (SARS-CoV-2). Similar to the other hypervirulent HCoVs, SARS-CoV-2 has a putative animal origin, likely descended from a related bat CoV that spilled over to humans either directly or after adaptation in another animal species, such as the Malayan pangolin (Lam et al., 2020). SARS-CoV-2 is highly related genetically (96% nt) to a SARS-like bat CoV (Zhou et al., 2020)

The SARS-CoV-2 induced disease, referred to as CoronaVirus Disease 2019 (COVID-19), affects the respiratory tract, with a number of patients displaying severe pneumonia and requiring hospitalisation and admission to intermediate or intensive care units. Unlike SARS and MERS, COVID-19 is characterised by low lethality rates and high frequency of asymptomatic or paucisymptomatic infections that likely favoured the spread of this new pandemic (Lai et al., 2020). As SARS-CoV-2 started spreading globally, between February and March 2020, potential spill over exposure (viral RNA) was noted in companion animals, likely due to their strict social interactions with humans. SARS-CoV-2 RNA was detected in two dogs and a cat without clinical signs in Hong Kong and in a cat with gastroenteric and respiratory signs in Bruxelles, all which lived in close contact with infected COVID-19

* Corresponding author at: Department of Veterinary Medicine, University of Bari Aldo Moro, Strada Prov. per Casamassima Km 3, 70010 Valenzano (BA), Italy.
E-mail addresses: nicola.decaro@uniba.it (N. Decaro), vito.martella@uniba.it (V. Martella), saif.2@osu.edu (L.J. Saif), canio.buonavoglia@uniba.it (C. Buonavoglia).

https://doi.org/10.1016/j.rvsc.2020.04.009

human patients.[1,2] This noted analogous findings observed during the 2002–2003 spread of SARS-CoV.[3]

2. Animal coronaviruses: the experience of veterinary medicine

Before the emergence of SARS-CoV, the first highly pathogenic HCoV, information was very scarce about HCoVs, whereas there was extensive knowledge in veterinary medicine about animal CoVs, their evolution and pathobiology. Infectious bronchitis virus (IBV) of poultry and feline infectious peritonitis virus (FIPV) have been known since the early 1900, representing animal examples on how CoVs can evolve, changing their tissue tropism and virulence (Decaro and Lorusso, in press). In addition, swine CoVs are paradigmatic on how CoVs may cross the species barriers infecting new hosts. Transmissible gastroenteritis virus of swine (TGEV, alphacoronavirus), likely originated from the closely related canine coronavirus (CCoV) (Lorusso et al., 2008) and in turn TGEV gave rise to the less virulent porcine respiratory CoV (PRCoV). Also, a TGEV-like CCoV was generated by recombination in the N terminal end of the S gene (Decaro et al., 2009). Two additional swine alphacoronaviruses emerged more recently, the porcine epidemic diarrhoea virus (PEDV) and the severe acute diarrhoea syndrome CoV (SADS-CoV), both derived from CoVs circulating in bats. The betacoronavirus porcine haemagglutinating encephalomyelitis virus (PHEV) was a derivative of bovine CoV, which in turn is believed to have descended from a bat virus through adaptation in a rodent species. More recently, porcine deltacoronavirus (PDCoV), the causative agent of severe diarrhoea outbreaks in North America and Asia, emerged from avian deltacoroviruses (Wang et al., 2019). The observed repeated events of inter-species transmission by animal CoVs rely on the exceptional ability of CoVs to expand their host range. This strongly supports the natural origin of SARS-CoV-2, confuting conspiracy theories of a laboratory origin (Liu et al., 2020).

Animal CoVs may also represent excellent host models for development of SARS-CoV-2 vaccines, which could require much more time than initially anticipated. The majority of vaccines licensed for the veterinary market have been developed for CoVs causing enteric infections, such as BCoV and the swine CoVs TGEV and PEDV. These vaccines are intended for parenteral use in pregnant cows/sows or oral use in sows (TGEV, PEDV) to transfer maternal immunity to their offspring and protect them in the first weeks of life, when they are more susceptible to severe of disease. These vaccines take advantage of different technologies, since BCoV/TGEV vaccines are inactivated or modified-live virus (MLV) formulations that are produced according to traditional protocols. For PEDV prophylaxis, in addition to killed and MLV preparations, vector-based vaccines expressing the spike protein are commercially available (Gerdts and Zakhartchouk, 2017; Saif, 2020). BCoV is also responsible for respiratory disease in 2–3 month-old calves or older animals, but specific vaccines currently are not available for prevention of the respiratory disease (Decaro et al., 2008). Also, some vaccines (i.e., CCoV) have been introduced into the market, used for years and later abandoned, after cost-effectiveness evaluations.[4] The CCoV vaccines were administered parenterally, induced good systemic but poor mucosal immunity and did not protect pups against infection with virulent virus (Pratelli et al., 2003, 2004; Decaro et al., 2011).

The only licensed animal CoV vaccines targeted to prevent respiratory CoV infections are IBV vaccines for chickens. These vaccines, administered parenterally, may not protect against the infection but they can reduce the severity of the respiratory signs and prevent involvement of the kidney and reproductive tract (Saif, 2020). One of the main issues of parenteral vaccination against respiratory CoVs in animals is that it does not trigger strong local immunity, usually represented by mucosal immunoglobulin A (IgA). Mucosal immunity, even if not preventing the infection, is able to reduce viral shedding (in terms of duration and extent) and the severity of the respiratory disease. Also this may be the case for SARS-CoV-2, which primarily affects the respiratory tract and, to a lesser extent, the enteric tract, with limited viremia and/or systemic involvement (Wong et al., 2020). Also, the duration of immunity elicited by natural infection with SARS-CoV-2 is not known yet. For animal CoVs, immunity after infection may be of short duration. For instance, feline enteric coronavirus (FECV) may induce short-term immunity that does not confer protection from reinfections. FECV is an avirulent biotype of feline coronavirus (FCoV) and it is the precursor of the hypervirulent biotype FIPV (Addie et al., 2020b). Interestingly, FIP vaccines are paradigmatic of how difficult the development of vaccines against human CoVs may be. FIP is a sporadic but highly lethal disease of cats that originates as a consequence of the switch from FECV to FIPV due to specific mutations in the spike protein gene (Chang et al., 2012). Despite considerable efforts so far, no effective FIPV vaccine has been developed. One of the main issues is that most experimental vaccines triggered an antibody-dependent enhancement (ADE) mechanism, which causes a more severe disease in immunised animals than in control cats after virus challenge (German et al., 2004). ADE is triggered by antibody-mediated virus entry into macrophages via Ig Fc receptors and might represent an obstacle to the development of SARS-CoV-2 specific vaccines (Rauch et al., 2018). An alternative mechanism for ADE has been described recently for MERS-CoV, for which neutralizing antibodies bind to the spike protein, triggering a conformational change of the spike and mediating viral entry into IgG Fc receptor-expressing cells through canonical viral-receptor-dependent pathways (Wan et al., 2020). Analogous to cats affected by FIP, in human patients with severe COVID-19, a cytokine storm syndrome is frequently observed that requires treatment of hyperinflammation to reduce fatality rates. This cytokine storm, which at the same time causes immunosuppression, is characterised by increased interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosis factor-α (Mehta et al., 2020). Notably, a similar cytokine pattern is observed in cats with FIP (Paltrinieri, 2008). Tocilizumab, an IL-6 receptor blocker monoclonal antibody, seems to be highly effective in reducing the severity of SARS-CoV-2 induced pneumonia (Favalli et al., 2020).

A number of antivirals have been tested to control FIP. After several unsuccessful attempts, research efforts have focused on two promising antiviral classes, namely protease inhibitors and nucleoside analogues, which inhibit viral replication either by blocking viral polyprotein cleavage or terminating viral RNA transcription. Treatment of cats with naturally occurring FIP with the 3C-like protease inhibitor GC376 induced a significant remission of disease signs and regression of lesions in 19/20 animals, although only six of these animals remained in remission for a long period (Pedersen et al., 2018). In contrast, long-term and repeated treatment with nucleoside analogue GS-441524 was successful in 25/26 cats with FIP, with only one animal not responding to retreatment (Pedersen et al., 2019). In addition, the same drug was able to stop faecal shedding of FECV in naturally infected cats (Addie et al., 2020a). Interestingly, a similar compound, the adenosine nucleoside monophosphate prodrug GS-5734, is the active molecule of remdesivir, largely employed as a potential antiviral against COVID-19. This drug was shown to be more effective than lopinavir, which, similar to GC376, acts against the viral 3C-like protease (Baden and Rubin, 2020).

[1] SciCoM - Comite Scientifique de l'Institué auprès de l'Agence Fédérale pour la Sécurité de la Chaîne Alimentaire, 2020. Risque zoonotique du SARS-CoV2 (Covid-19) associé aux animaux de compagnie: infection de l'animal vers l'homme et de l'homme vers l'animal (SciCom 2020/07). www.afsca.be.

[2] https://www.scmp.com/news/hong-kong/health-environment/article/3077802/coronavirus-pet-cat-hong-kong-tests-positive

[3] Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). https://apps.who.int/iris/handle/10665/70863

[4] https://www.aaha.org/globalassets/02-guidelines/canine-vaccination/vaccination_recommendation_for_general_practice_table.pdf

3. Conclusions

Considering the long-term experience gained with animal CoVs, veterinary medicine could help to forge a better understanding of the origin and spread of SARS-CoV-2 and drive future research in human medicine towards the development of immunogenic and safe vaccines and effective antiviral drugs. The successes and failures encountered with prophylaxis and treatment of animal CoV diseases, such as FIP, might be useful to address issues related to COVID-19 in a One Health approach. Likewise the atypical pneumonia evident in pigs infected with PRCV, despite mild clinical signs, and the pneumonia in cattle triggered by BCoV in complex with respiratory bacteria and the stress of transport, may provide models to understand factors that precipitate severe pneumonia in COVID-19 patients.

Progressive deforestation and anthropization of natural environments have largely compromised some ecological niches where CoVs of wildlife are usually confined. Also, human consumption of endangered wildlife, even if not demonstrated to play a role in the onset of SARS-CoV-2, should be restricted or banned, particularly in the unsanitary conditions prevalent in live animal markets. Considering that animal CoVs spilled over into humans in three different occasions in the short time span of two decades, a more reverent management of the environment will be fundamental to prevent future emergence of pandemic CoVs. Under these circumstances, veterinary medicine should support policy makers to adopt and promote sound and sustainable measures for management of the environment and of animals and advance the global 'One Health' movement.

References

Addie, D.D., Curran, S., Bellini, F., Crowe, B., Sheehan, E., Ukrainchuk, L., Denaro, N., 2020a. Oral Mutian®X stopped faecal feline coronavirus shedding by naturally infected cats. Res. Vet. Sci. 130, 222–229.

Addie, D., Houe, L., Maitland, K., Passantino, G., Decaro, N., 2020b. Effect of cat litters on feline coronavirus infection of cell culture and cats. J. Feline Med. Surg. 22, 350–357.

Baden, L.R., Rubin, E.J., 2020. Covid-19 - the search for effective therapy. N. Engl. J. Med. doi. https://doi.org/10.1056/NEJMe2005477.

Buonavoglia, C., Decaro, N., Martella, V., Elia, G., Campolo, M., Desario, C., Castagnaro, M., Tempesta, M., 2006. Canine coronavirus highly pathogenic for dogs. Emerg. Infect. Dis. 12, 492–494.

Chang, H.W., Egberink, H.F., Halpin, R., Spiro, D.J., Rottier, P.J., 2012. Spike protein fusion peptide and feline coronavirus virulence. Emerg. Infect. Dis. 18, 1089–1095.

Decaro, N., Lorusso, A., 2020. Novel human coronavirus (SARS-CoV-2): a lesson from animal coronaviruses. Vet. Microbiol (in press).

Decaro, N., Campolo, M., Desario, C., Cirone, F., D'Abramo, M., Lorusso, E., Greco, G., Mari, V., Colaianni, M.L., Elia, G., Martella, V., Buonavoglia, C., 2008. Respiratory disease associated with bovine coronavirus infection in cattle herds in southern Italy. J. Vet. Diagn. Investig. 20, 28–32.

Decaro, N., Mari, V., Campolo, M., Lorusso, A., Camero, M., Elia, G., Martella, V., Cordioli, P., Enjuanes, L., Buonavoglia, C., 2009. Recombinant canine coronaviruses related to transmissible gastroenteritis virus of swine are circulating in dogs. J. Virol. 83, 1532–1537.

Decaro, N., Mari, V., Sciarretta, R., Colao, V., Losurdo, M., Catella, C., Elia, G., Martella, V., Del Giudice, G., Buonavoglia, C., 2011. Immunogenicity and protective efficacy in dogs of an MF59™ adjuvanted vaccine against recombinant canine/porcine coronavirus. Vaccine 29, 2018–2023.

Favalli, E.G., Ingegnoli, F., De Lucia, O., Cincinelli, G., Cimaz, R., Caporali, R., 2020. COVID-19 infection and rheumatoid arthritis: faraway, so close!. Autoimmun. Rev. 20, 102523.

Gerdts, V., Zakhartchouk, A., 2017. Vaccines for porcine epidemic diarrhea virus and other swine coronaviruses. Vet. Microbiol. 206, 45–51.

German, A.C., Helps, C.R., Harbour, D.A., 2004. FIP: a novel approach to vaccination. In: Proceedings from the 2nd international FCoV/FIP Symposium, Glasgow, 4-7 august 2002. J. Feline Med. Surg, pp. 119–124 2004 Apr;6.

Lai, C.C., Liu, Y.H., Wang, C.Y., Wang, Y.H., Hsueh, S.C., Yen, M.Y., Ko, W.C., Hsueh, P.R., 2020. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths. J. Microbiol. Immunol. Infect. 1182 (20), 30040–30042 Pii: S1684.

Lam, T.T., Shum, M.H., Zhu, H.C., Tong, Y.G., Ni, X.B., Liao, Y.S., Wei, W., Cheung, W.Y., Li, W.J., Li, L.F., Leung, G.M., Holmes, E.C., Hu, Y.L., Guan, Y., 2020. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. Nature. https://doi.org/10.1038/s41586-020-2169-0. 2020 Mar 26.

Liu, S.L., Saif, L.J., Weiss, S.R., Su, L., 2020. No credible evidence supporting claims of the laboratory engineering of SARS-CoV-2. Emerg. Microbes Infect. 9, 505–507.

Lorusso, A., Decaro, N., Schellen, P., Rottier, P.J., Buonavoglia, C., Haijema, B.J., de Groot, R.J., 2008. Gain, preservation, and loss of a group 1a coronavirus accessory glycoprotein. J. Virol. 82, 10312–10317.

Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J.; HLH Across Speciality Collaboration, UK, 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet pii: S0140-6736(20)30628–0.

Paltrinieri, S., 2008. The feline acute phase reaction. Vet. J. 177, 26–35.

Pedersen, N.C., Kim, Y., Liu, H., Galasiti Kankanamalage, A.C., Eckstrand, C., Groutas, W.C., Bannasch, M., Meadows, J.M., Chang, K.O., 2018. Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis. J. Feline Med. Surg. 20, 378–392.

Pedersen, N.C., Perron, M., Bannasch, M., Montgomery, E., Murakami, E., Liepnieks, M., Liu, H., 2019. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis. J. Feline Med. Surg. 21, 271–281.

Pratelli, A., Tinelli, A., Decaro, N., Cirone, F., Elia, G., Roperto, S., Tempesta, M., Buonavoglia, C., 2003. Efficacy of an inactivated canine coronavirus vaccine in pups. New Microbiol. 26, 151–155.

Pratelli, A., Tinelli, A., Decaro, N., Martella, V., Camero, M., Tempesta, M., Martini, M., Carmichael, L.E., Buonavoglia, C., 2004. Safety and efficacy of a modified-live canine coronavirus vaccine in dogs. Vet. Microbiol. 99, 43–49.

Rauch, S., Jasny, E., Schmidt, K.E., Petsch, B., 2018. New vaccine technologies to combat outbreak situations. Front. Immunol. 9, 1963.

Saif, L.J., 2020. Vaccines for COVID-19: perspectives, prospects, and challenges based on candidate SARS, MERS, and animal coronavirus vaccines. Euro. Med. J. https://doi.org/10.33590/emj/200324.

Wan, Y., Shang, J., Sun, S., Tai, W., Chen, J., Geng, Q., He, L., Chen, Y., Wu, J., Shi, Z., Zhou, Y., Du, L., Li, F., 2020. Molecular mechanism for antibody-dependent enhancement of coronavirus entry. J. Virol. 94 (5) Pii: e02015-19.

Wang, Q., Vlasova, A.N., Kenney, S.P., Saif, L.J., 2019. Emerging and re-emerging coronaviruses in pigs. Curr. Opin. Virol. 34, 39–49.

Wong, S.H., Lui, R.N., Sung, J.J., 2020. Covid-19 and the digestive system. J. Gastroenterol. Hepatol. https://doi.org/10.1111/jgh.15047.

Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y., Xiao, G.F., Shi, Z.L., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273.