BLINDNESS, LIGHT, AND THE COVID-19 PANDEMIC

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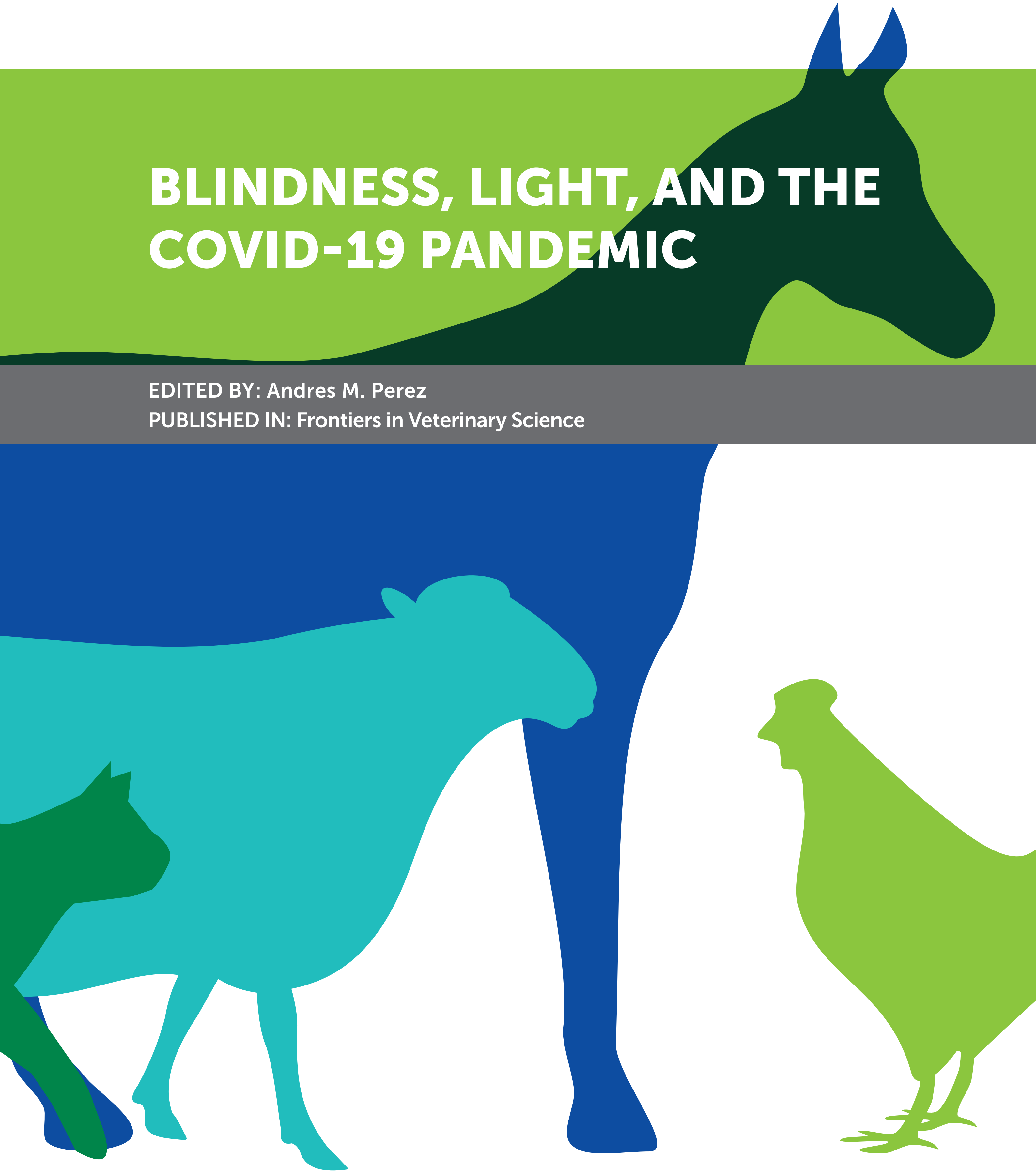

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BLINDNESS, LIGHT, AND THE COVID-19 PANDEMIC

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EDITORIAL
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Editorial: Blindness, Light, and the COVID-19 Pandemic

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Editorial on the Research Topic

Blindness, Light, and the COVID-19 Pandemic

In 1995, Nobel Laureate Jose Saramago published *Blindness* (*Ensaio sobre a cegueira* in Portuguese), a novel that describes the effects of a mass epidemic of blindness. Unlike Saramago's book, in which the cause of such sudden condition remained unexplained, the agent causing the most devastating human pandemic in recent history, referred to as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been fully characterized shortly after its first identification in late 2019 in Wuhan, China. Coronaviruses are relatively novel threats to public health. However, veterinarians have a long-standing experience in fighting diseases caused by this family of RNA viruses. Furthermore, mass epidemics have recently affected animals more frequently than humans and for that reason, many veterinarians have had the chance to experience the complexities associated with dealing with emergencies that resemble the challenges associated with the coronavirus disease (COVID-19) pandemic.

In response to this health crisis, probably for the first time in history, the scientific community was in the spotlight. However, public attitudes and opinions toward science were heavily polarized and influenced by political, social, and philosophical views. While many looked at science as a source of answers and a resource for data and information that enable better understanding, and ultimately control and prevention of the disease, there was also miscommunication, skepticism, and even social revelry. In the middle of such complex social, economical, and political scenarios, and while the scientific community engaged in an unprecedented race for discovery, from the onset of the pandemic, veterinarians placed themselves at the forefront of that fight. Veterinary Clinics and hospitals were adapted to fulfill protocols and mitigate risks while still taking care of their mission, veterinary laboratories were adapted to aid with the diagnosis and molecular characterization of the SARS-CoV-2, human and financial resources were shifted to support research aimed at helping with the control and prevention of the disease. To honor the efforts of veterinarians around the globe, the World Veterinary Association (WVA) dedicated the 2021 World Veterinary Day (April 24) to celebrate the work of veterinarians to protect animal and human health during the COVID-19 pandemic (https://www.worldvet.org/news.php?item=465). This Research Topic by Frontiers in Veterinary Science joins that celebration, bringing together a collection of 12 scientific papers representing stories, opinions, perspectives, and research results that illustrate the impact that the COVID-19 pandemic has caused on veterinary sciences and veterinarians. Papers have been grouped into three major areas, illustrating how the pandemic has (a) impacted our perspectives for veterinary public health and one health, (b) affected animal welfare and the operation of veterinary services, and (c) promoted novel research initiatives and opportunities, respectively.

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(A) VETERINARY PUBLIC HEALTH AND ONE HEALTH

Although the benefits of the coexistence of animals and humans have traditionally exceeded the negative consequences of such interaction, in recent decades, human population growth and efforts to alleviate poverty and hunger have led to an increase in the magnitude and complexity of such interactions, affecting widespread and disparate geographies and a variety of animal species. Consequently, there was a dramatic increase in the risk for the emergence and transmission of diseases in the human-animal interface. There is an urgent need to search for, identify, and characterize potential sources of emerging pathogens at the animal-human interface and to develop strategies to prevent or mitigate the risk for future pandemics (Magouras et al.). The extent and complexity of the human-animal interaction have also been affected, in some places, by an increase in the legal and illegal trade of wildlife for consumption, which, in addition to increasing the risk for disease transmission, has impaired access to resources for native communities around the world, which typically rely on wild meat to meet their nutritional requirements (Walzer). However, silver bullets do not exist and solutions are difficult to design and implement; indeed, there is a risk that restrictive measures to trade, imposed in an attempt to reduce the likelihood of diseases spreading, would affect food security further, adding to the damage that the pandemic has caused to global food access (Mardones et al.).

(B) ANIMAL WELFARE AND OPERATION OF VETERINARY SERVICES

COVID-19 outbreaks have had devastating consequences for some activities, particularly those conducted in confined spaces in which workers are located close to each other, such as meat processing plants. The capacity of pig processing plants in the U.S. was reported to have decreased by 45% at a given time during the epidemic, representing a daily reduction of ∼250,000 animals in the country's capacity to slaughter pigs. The situation severely affected animal welfare, in the form of longer transportation times to process pigs in plants that were still active, culling of animals in farms, and the potential environmental impact associated with the disposal of those carcasses (Marchant-Forde and Boyle). In response to the crisis, in many countries, multisectoral groups were established in an attempt to mitigate the impact of the pandemic on animal welfare. For example, a group of organizations in Australia outlined recommendations aimed at protecting animal welfare in the country and promoting similar actions in other regions (Baptista et al.).

Veterinary clinics, hospitals, and laboratories have also been affected by the pandemic, with regular function and activity disrupted in many complex ways. Challenges included, for example, partial or complete shutdowns, interrupted courier services, disruptions in workflow and diagnostic testing, and the need to adapt laboratories to new physical distancing practices, protocol development or enhancement for handling samples from high risk or susceptible species, and fulfilling requirements for pre-test permission approval from state and federal veterinary agencies (Stokol et al.).

(C) EMERGING OPPORTUNITIES AND CONSEQUENCES FOR VETERINARY RESEARCH

On the other hand, the COVID-19 pandemic also inspired and promoted research initiatives emerging from veterinary sciences throughout the world, with the objective of aiding control of the emergency under a One Health umbrella. In the interface of animal and public health, there is an opportunity for the knowledge and experiences emerging from veterinary sciences to accelerate response and preparedness against COVID-19 and other potential emerging threats (Mobasheri).

One potential area of collaboration is rooted in the basic and applied research conducted for decades in the veterinary field to develop antivirals and immune modulators to help control the diseases caused by coronaviruses in animals. For example, recombinant bovine gamma interferon (rbIFN-λ) was found to be effective in preventing SARS-CoV-2 infection in VERO cells (Cardoso et al.). Similarly, animal models of coronavirus infections can help understand the pathogenesis and implications of the disease in humans. For example, neurological signs have been reported in human cases of COVID-19, while, recently, there have been promising results in the use of antiviral drugs for the treatment of the neurological form of coronavirus infection in cats (Dickinson). In addition to animal models, epidemiological models originally developed for animal diseases were adapted to help explain and predict the spread of COVID-19 in human populations (Halasa et al.).

Successful initiatives to support this response through a collaborative One Health approach were launched, including, for example, the parameterization of mathematical models of COVID-19 spread in Ireland, leverage of public and veterinary epidemiology resources to support the response to the pandemic in Australia, and multinational collaboration to create a platform for knowledge exchange in sub-Saharan Africa (Häsler et al.). In a broad context, many lessons learned from the management of animal health emergencies could have helped and should be adopted in the future, anticipating further global failure, which has already been experienced in addressing the COVID emergency, stressing an urgent to revisit a global strategy for implementation of the One Health agenda (Enticott and Maye).

In conclusion, similar to the character that escaped blindness, who was able to see during the epidemic described in Saramago's fictional novel, we expect that the collection here illustrates the light that veterinary sciences may bring in the form of reflection, and the generation of the foundational knowledge required to develop tools and strategies for fighting one of the most impactful health challenges experienced in our recent history, while increasing preparedness and mitigating the risk for, and impact of, future global emergencies.

AUTHOR CONTRIBUTIONS

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COVID-19, Companion Animals, Comparative Medicine, and One Health

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The COVID-19 pandemic in 2020 has stimulated open collaboration between different scientific and clinical disciplines like never before. Public and private partnerships continue to form in order to tackle this unprecedented global challenge. This paper highlights the importance of open collaboration and cooperation between the disciplines of medicine, veterinary medicine, and animal health sciences in the fight against COVID-19. Since the pandemic took the whole world by surprise, many existing drugs were rapidly repurposed and tested in COVID-19 clinical trials and some of the trials are revealing promising results, it is clear that the long-term solution will come in the form of vaccines. While vaccines are being developed, the antiviral agent Remdesivir (RDV, GS-5734) is being repurposed for use in human clinical trials but this is being done without acknowledging the significant efforts that went into development for treating cats with feline infectious peritonitis (FIP), a highly fatal immune-mediated vasculitis in cats which is caused by a feline coronavirus. There are many other antiviral drugs and immune modulating treatments that are currently being trialed that have animal health origins in terms of discovery and clinical development. Closer collaboration between the animal health and human health sectors is likely to accelerate progress in the fight against COVID-19. There is much that we do not yet know about COVID-19 and its causative agent SARS-CoV-2 but we will learn and progress much faster if we increase interdisciplinary collaboration and communication between human and animal health researchers and taking a genuine "One Health" approach to this and other emerging viral pathogens. Enhanced knowledge of zoonotic coronaviruses can significantly enhance our ability to fight current and future emerging coronaviruses. This article highlights the acute need for One Health and comparative medicine and the crucial importance of building on and recognizing veterinary research for addressing future human pandemics.

Keywords: COVID-19, SARS-CoV2, companion animal, zoo animal, One Health, comparative medicine, Remdesivir (RDV, GS-5734)

INTRODUCTION

COVID-19 is a new respiratory illness in humans that affects the lungs and the airways (1). It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). In late December, 2019, an outbreak of COVID-19 was reported in Wuhan, China (3). Despite early warning about its contagious nature, SARS-CoV-2 has now spread across the globe (4), infecting more than two million people and claiming more than 243,000 lives (on 2 May 2020)[1] On 11 March 2020, the World Health Organization (WHO), declared COVID-19 as a pandemic[2], which is defined as the worldwide spread of new disease with major public health implications. There are some reports that the original outbreak predated December 2019 and there is emerging evidence to support this assertion.

Although COVID-19 is an emerging, rapidly evolving situation, clinical studies carried out in the last 5 months have revealed a great deal about its clinical manifestations and sequalae. The main symptoms of coronavirus (COVID-19) are fever, fatigue, continuous cough, and expectoration (sputum production) (5). The disease affects both lungs and most patients exhibit lymphopenia, increased levels of C-reactive protein (CRP), and elevated erythrocyte sedimentation rate (ESR) (5). The main clinical complications for COVID-19 patients are acute respiratory distress syndrome (ARDS) (6), which is associated with the "cytokine storm" syndrome, the uncontrolled production of pro-inflammatory mediators that contribute to ARDS (7).

The virus is highly contagious and airborne. It is spread by human-to-human transmission *via* droplets or direct contact (8). Person-to-person transmission is presumed and it is suspected to be carried by asymptomatic carriers (9). It is suspected to cause long-lasting lung damage, characterized by fibrosis. Core biopsies from post-mortem samples have revealed fibroblastic proliferation with extracellular matrix degradation and fibrin forming clusters in airspaces has been reported in (10). Other than increased CRP and elevated pro-inflammatory cytokines such as tumor necrosis factor a (TNF- a) and interleukin-6 (IL-6) (11) there are currently no biomarkers that can accurately predict clinical outcomes but some patients exhibit "dramatically" high levels of D-dimer, a by-product of blood coagulation (12, 13). Significantly higher levels of D-dimer and CRP indicate that these two proteins may be measured in combination as biomarkers of disease severity (14, 15).

In terms of treatment, there is hope for several existing antiviral agents, repurposed drugs, including a new trial that includes the use of dexamethasone[3], and immune modulating treatments that are currently being trialed (7) and several vaccines are in development (16). Understanding immune evasion strategies of SARS-CoV2 and the resulting delayed but massive immune response and ARDS should no doubt result in the identification of disease biomarkers that predict outcomes as well as phenotype and disease stage specific treatments that will likely include both antiviral and immune modulating agents. However, it is unlikely that the above mentioned biomarkers can be used to guide treatments as the development of treatments needs to be massively accelerated to reduce the mortality rate associated with COVD-19. Another important strategy is closer co-operation between the medical, veterinary, and animal health disciplines.

This perspective article highlights the importance of taking a "One Health" approach and broader, more active and more concerted collaboration and cooperation between the disciplines of medicine, veterinary medicine, and animal health sciences in the fight against COVID-19. It is important to mention that many drugs used in human medicine were initially developed using animal models and some drugs, including Remdesivir, have been repurposed from veterinary medicine to human medicine (see later).

ONE HEALTH APPROACH TO STUDYING COVID-19 AND SARS COV-2

One Health represents the collaborative efforts of multiple scientific and clinical disciplines working to attain optimal health for humans, animals, and the environment. My own unique perspective on this topic comes from my basic training in biochemistry and physiology. When a new pathogen is identified, biochemists and molecular biologist have a tendency to focus on genetic sequence and structure, and use comparative approaches to Study the new pathogen in the context of existing knowledge of similar pathogens. A good place to start is the genetic sequence of the virus and the amino acid sequence of its spike proteins, which may turn out to be important antigens and targets for development of vaccination strategies. After learning more about the sequence and the structure of the virus, return to immunology to look for ways to develop immunity to it. Let's begin with the sequence of the spike proteins. There is significant amino acid sequence homology between the spike protein epitopes of taxonomically-related coronaviruses (17). Can this knowledge help in the development of novel treatments for COVID-19? Based on the high-homology between the spike protein epitopes it has been hypothesized that past contact with infected animals may shield some humans against the circulating SARS-CoV-2 (17). This is a very interesting hypothesis that requires further attention. Since other coronaviruses can infect other animals such as cats, dogs, mice, rats, cattle, and bats, their pivotal role as "virus reservoir" needs to be considered further. Co-existence between humans and animals needs to be studied more closely because animals that have been infected with other species of coronavirus, including companion animals might act as a "beneficial" source of immune-stimulating virus particles; thus shielding against the circulating SARS CoV-2 in humans (17). However, further epidemiological and experimental studies are required to test this hypothesis. This idea is not implausible and the pioneering work that Edward Jenner did two centuries ago reminds us that taking a "One Health" approach can be extremely valuable (18). Jenner's discovery of the link between cowpox in

[1] https://www.covidvisualizer.com
[2] https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020
[3] https://www.recoverytrial.net

cattle and smallpox in humans helped to lay the foundations of immunology and vaccinology, creating the first ever live vaccine: the smallpox vaccine (19).

CANINE CORONAVIRUSES

It is important to note that canine respiratory coronaviruses are not the same as the SARS CoV-2 responsible for the COVID-19 pandemic in the human population. Dogs have had to co-evolve with their own respiratory and enteric coronaviruses. The Coronaviridae Study Group of the International Committee on Taxonomy of Viruses is the group responsible for developing the classification of viruses and taxon nomenclature of the family *Coronaviridae*. This group has recently assessed the placement of the human pathogen, tentatively named 2019-nCoV, within the Coronaviridae, providing an updated classification of the phylogeny and taxonomy of coronaviruses (2). Canine respiratory coronavirus (CRCoV) is a coronavirus of dogs, which is widespread in North America, Japan, and across Europe (20). CRCoV was detected in dogs more than 14 years ago (21). It has been associated with respiratory disease, particularly in kennel dog populations (20). The virus is highly pathogenic, causing severe lesions (22). It is genetically and antigenically distinct from enteric canine coronaviruses (23, 24), a finding which has stimulated further epidemiological research, serological surveys, and the development of new diagnostic tests. It is not clear, at this stage, if prior human exposure to CRCoV can afford any protection against later exposure to SARS CoV-2. Further research studies are required to determine if humans that co-exist with canine companions that have previously been exposed to CRCoV might develop a stronger immunity to SARS CoV-2 to those who have not had this exposure. This is purely speculative and requires further exploration.

CAN SARS-COV-2 INFECT COMPANION AND ZOO ANIMALS?

There has been a great deal of interest in the press about companion and zoo animals serving as reservoirs for SARS-CoV-2. It has been suggested that SARS-CoV-2 can infect cats but not dogs (25). Cats may be infected with SARS CoV-2, the coronavirus that causes COVID-19 and spread it to other cats, but according to researchers in China, dogs are not susceptible to the infection. The team at Harbin Veterinary Research Institute in China has proposed that chickens, pigs, and ducks are not likely to catch the virus. However, since COVID-19 is an emerging and rapidly evolving pandemic with the potential to use animals as reservoir hosts. There are quite a few recent reports[4] about SARS-CoV-2 infections in mink and ferrets and linked cases of COVID-19 in humans at Dutch fur farms (26). This remind us of previous outbreaks of avian influenza virus H9N2 infections in farmed mink (27). Beyond mink and ferrets, we simply do not know much more at this stage. However, transmission from humans to dogs, domestic cats, tigers, and lions has indeed occurred. Furthermore, pigs, cats, ferrets (28), and primates have been identified as good candidates for susceptibility to SARS-CoV-2 (29). It is important to point out that SARS-CoV-2 is not originally a human virus. SARS-CoV-2 belongs to β-coronavirus family and the sequencing studies carried out so far suggest that the virus in humans is identical to the horseshoe bat coronavirus, pointing to bat as the natural, and reservoir host (16). The SARS-CoV-2 genome is closest to that of severe acute respiratory syndrome-related coronaviruses from horseshoe bats, and its receptor-binding domain is closest to that of pangolin coronaviruses (30). However, it has been proposed that the recent outbreak of COVID-19, did not come directly from pangolins (31). Recent studies also suggested that *Bovidae* and *Cricetidae* should be included in the screening of intermediate hosts for SARS-CoV-2 and could be unexplored reservoir hosts (32). The current gaps in knowledge highlight the need for field studies in the same geographical regions where the SARS-CoV-2 emerged, to look for intermediate hosts and to establish if there are any animal species that we have missed.

THE ANIMAL HEALTH ORIGIN OF REMDISIVIR

Remdesivir (RDV, GS-5734) is a broad-spectrum antiviral drug developed by the biopharmaceutical company Gilead Sciences that is currently being tested as a potential treatment for COVID-19 in international, multi-site clinical trials (33). The development of RDV was originally started by veterinary and animal professionals and focused on treating cats with feline infectious peritonitis (FIP) but this fact has been largely ignored by the press and almost forgotten by the scientific community. This is not an uncommon problem in science especially when disciplines remain focused on their own fields and do not communicate more widely. There are numerous examples of the benefits of taking a "One Health" approach in developing new therapeutics and novel medicines.

FIP is quite a rare and unusual disease in the cat caused by certain strains of the feline coronavirus. Most strains of feline coronavirus are enteric and found in the gastrointestinal tract. These enteric strains do not cause significant disease. However, in ∼10% of cats infected with enteric strains of feline coronavirus, one or more mutations in the virus alter its biological behavior, resulting in leucocytes becoming infected and when this occurs, the disease is referred to as the FIP. An intense inflammatory reaction to FIP occurs around vessels in the tissues where these infected cells locate, often in the abdomen. Similar to the severe cases of SARS-CoV-2 infection in humans resulting in ARDS and over-activation of the immune system, the immune system of the cat can become over-stimulated, resulting in the development of FIP, and once a cat develops clinical FIP, the disease is usually progressive and almost always fatal without treatment, in this case Remdesivir. This is precisely why there is so much interest in the repositioning of this drug for treating SARS-CoV-2. However, Gilead Sciences is now repositioning RDV for the treatment of COVID-19 but without mentioning the significant

[4]https://www.sciencemag.org/news/2020/06/coronavirus-rips-through-dutch-mink-farms-triggering-culls-prevent-human-infections

feline coronavirus research that led to its development. The available data on the breadth and potent antiviral activity of RDV (including both contemporary human and highly divergent zoonotic coronaviruses) can significantly enhance our ability to fight current and future emerging coronaviruses (34). According to the European Medicines Agency (EMA), Remdesivir is the first biological drug against COVID-19 to be recommended for authorization in the EU. EMA's human medicines committee (CHMP) has recommended granting a conditional marketing authorization to Remdesivir for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen[5] This is a wonderful exemplar of the need for a "One Health" approach and the importance of building on and recognizing veterinary research for addressing human pandemics (35). Drug repurposing is a reality in the pharmaceutical industry, the anthelmintic drug Ivermectin is another good example, and it can provide huge savings in valuable time and research and development budgets.

CONCLUSION

Coronaviruses are a diverse group of viral pathogens. Although some of them are potentially dangerous zoonotic pathogens, many are not pathogenic. These viruses possess rapidly evolving genomes and are finding new hosts (36). In the last two decades three coronaviruses have crossed the species barrier and caused human epidemics. We have been completely unprepared for these epidemics. One of these was the recently emerged SARS-CoV-2. We were totally unprepared for the current COVID-19 pandemic. However, there were scientific papers published more than 10 years ago that predicted the emergence of such an airborne coronavirus. Nevertheless, we ignored the classic literature and we did this at our peril. A review article published in 2007, 13 years before the current COVID-19 crisis predicted this pandemic (37). The authors from the University of Hong Kong did not possess a crystal ball. Instead, they had great insight and predicted that the coronavirus would, 1 day, pose a global threat. They wrote: "The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb."

Climate change and globalization are driving the destruction of natural habitats which brings humans into much closer contact with wildlife. Another example is the Nipah and Hendra virus, a virus in bats that is also transmitted the humans via intermediate hosts (38). The previous findings that horseshoe bats are the natural reservoir for SARS-CoV-like virus and that civets are the amplification host highlight the importance of wildlife and biosecurity in farms and wild animal markets. Wild animals can serve as the reservoirs and for emerging infectious diseases. There is much that we do not know about COVID-19 and the causative agent SARS-CoV-2. However, we are unlikely to progress fast unless we enhance interdisciplinary collaboration and communication (39) and take a genuine One Health approach to this and related viral pathogens. In conclusion, we will make much greater progress if we enhance collaboration and communication between human and animal health researchers, viral disease experts, wildlife ecologists, and even geographers to take a "One Health" approach to this and other emerging viral pathogens. This is not merely a battle, we are entrenched in a long-term conflict that is largely the result of human industrialization and globalization. This is a long-term conflict that cannot be won by human and animal medicine alone.

[5]https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Prediction Models in Veterinary and Human Epidemiology: Our Experience With Modeling Sars-CoV-2 Spread

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The worldwide outbreak of Sars-CoV-2 resulted in modelers from diverse fields being called upon to help predict the spread of the disease, resulting in many new collaborations between different institutions. We here present our experience with bringing our skills as veterinary disease modelers to bear on the field of human epidemiology, building models as tools for decision makers, and bridging the gap between the medical and veterinary fields. We describe and compare the key steps taken in modeling the Sars-CoV-2 outbreak: criteria for model choices, model structure, contact structure between individuals, transmission parameters, data availability, model validation, and disease management. Finally, we address how to improve on the contingency infrastructure available for Sars-CoV-2.

Keywords: modeling, infectious, disease, spread, COVID-19

INTRODUCTION

Infectious diseases are a constant threat for public health and consequently also the economy. Although hygiene measures have been well-established and efficient prevention and control measures such as vaccines have been developed for many diseases, only one human disease (smallpox) and one animal disease (Rinderpest) have been eradicated (1). On the other hand, new diseases are emerging and re-emerging in several parts of the world in both humans (e.g., COVID-19) and animals [e.g., African swine fever (ASF)]. It is therefore important to have consistent and effective systems for rapid and successful control of infectious diseases of both humans and animals. Models of infectious diseases have been used for many years to understand the dynamics of these diseases and to support decision making, and are used in both animal and human populations (2, 3). There is a large overlap with regard to methodology, procedures, and general epidemiological considerations when modeling infectious diseases of animals and humans. The development of models in both contexts is also similarly challenged by several factors such as the availability of data, understanding of the disease and host behavior, and external factors such as the environment.

At the start of the SARS-CoV-2 outbreak in Denmark, an expert group of modelers was established to develop models to predict the course of the epidemic. The authors were part of this group due to their previous experience with modeling disease spread mostly within the veterinary field. In this study, we discuss and compare the challenges for infectious disease prediction models of animal and human populations based on our experience in modeling infectious diseases in animals [e.g., foot-and-mouth disease (FMD), ASF, and bluetongue virus (BTV)] and our recent experience of modeling the spread of SARS-CoV-2 in humans.

CHOICE OF MODELING METHOD

Several modeling methods can be used to mimic the spread of infectious diseases, depending on the disease itself, available data, the need for details, and the purpose of the model (2, 4). Traditionally, ordinary differential equation (ODE) models have been popular, but with increasing computational power, agent-based models (ABMs) that can include higher levels of detail are increasingly being used (4). The purpose of the model is key to the choice of model.

Models are simple representations of real-life systems. In order to be able to build a model that properly represents a given system, it is necessary to have key knowledge in place: (1) a fairly good understanding of how the disease is spread (or knowledge of similar diseases, as for instance for SARS in relation to COVID-19); (2) background data on the host population (demography, density, etc.); and (3) data on the behavior of the host population (mixing patterns). There are two main phases of required models in an outbreak situation for a new disease like COVID-19. During the initial phase where a lockdown of large parts of society is implemented, it is important to have one or more models that can: (1) include the available number of parameters, which are often minimal in number due to the lack of necessary data at the early stage of the epidemic, and (2) run reasonably fast, in order to provide timely predictions on a national/regional level where large number of individuals may be involved. The purpose of modeling in this phase is to evaluate the current (lockdown) situation. In the second phase, where the focus regarding Sars-CoV-2 has been on how to reopen society, it is also important (1) that it is relatively easy to adjust the models to include newly arising information during the outbreak and (2) that the models are flexible and detailed enough to include information on the relevant parts of society.

During the 2001 FMD epidemic in the UK, an ABM with the farm as the modeling unit was used to advise the authorities on the control of the disease (5). Similarly, for the first BTV outbreaks in northern Europe in 2006, models were used to inform authorities on how to react with regard to early warning, mitigation of impact, vaccinating animals, and testing for freedom of disease (6, 7). Another example is the ASF virus genotype II that has persisted in Europe since 2007 and spread to other parts of the world (8). An ABM for the spread of ASF within wild boar populations has been used to advise the European authorities in the control of the disease (9, 10).

In the current Sars-CoV-19 pandemic, many simulation models have been developed, including both ODE and ABM models, of which some have been used to advise authorities. For instance, an ABM was used in the UK to guide the lockdown of the country (11). In the USA, several models were developed and used by the CDC individually or as ensemble modeling to predict the spread of Sars-CoV-19 on a state or country level (12). In Sweden, an ODE model has been used to advise the authorities during the epidemic (13), while a stochastic meta-population model was used in Norway (14). In Denmark, an ODE model was used to advise the authorities (https://github.com/laecdtu/C19DK) and qualitatively supported by an ABM. For previous human epidemics, such as measles, SARS, and influenza, ABM, and ODE models were developed to study disease dynamics and/or guide the control of the epidemics [see details in a review (3)].

DATA ON CONTACT STRUCTURE

One of the main challenges in modeling disease spread is identifying and obtaining data on contact structure between the modeled units (e.g., individuals or farms), when heterogeneity is considered. In the veterinary field, the spread of a disease is usually modeled either based on physical contacts between the modeled units (15) or using distance-based kernels (5). In the models that simulate the spread of diseases in the veterinary field using explicit contacts, the spread is driven by contacts between farms via animal movements, indirect contacts (e.g., veterinarians and vehicles), and/or vectors (midges for BTV, air for FMD, and wild boar for ASF). Several countries maintain registers for animal movements between herds, allowing explicit modeling of disease spread between herds (16). Data on indirect contacts is available based on questionnaires and field studies (17). For diseases that spread via vectors, data are provided via experiments and field studies (18–21). For airborne spread, meteorological data have been used to study the spread of FMD (22).

Because humans can normally move freely, while livestock populations are restricted to their farms, humans are more heterogeneous in their activities and contact patterns. Modeling this heterogeneity is therefore important to mimic disease spread correctly. We found few comprehensive studies quantifying contacts and contact patterns between individuals (23–26). These contacts formed the backbone for modeling the spread of Sars-CoV-2 in several models such as [https://github.com/laecdtu/C19DK; (27–29)].

DATA ON DISEASE STAGES AND TRANSMISSION

In the veterinary field, data on the manifestation and stages of infectious diseases within an individual animal and the transmission between individual animals are normally collected based on highly controlled experimental studies (30–32). Such studies are necessary in order to understand and quantify transmission and hence reliably use the data in models of disease spread and control.

In the current Sars-CoV-19 pandemic, data from previous epidemics with other similar viruses such as SARS and influenza were used to parametrize models published at earlier stages (33). Later on, data specifically about Sars-CoV-2 became available from multiple sources (patients, contact tracing, special situations such as cruise ships) allowing the estimation of necessary information regarding disease stages, manifestation, and transmission potential between individuals (34–37). Nevertheless, important information such as proportion of asymptomatic cases, infectiousness and susceptibility of children and their role in disease spread, and the role of superspreaders and superspreading events is yet to be unraveled.

DATA FOR MODELING AND VALIDATION

A general aspect when modeling infectious diseases in real time is fitting models to the available disease occurrence data. For instance, during the 2001 FMD epidemic in the UK, infection spread was modeled by creating a spread kernel using the observed outbreak data (5). Similarly, the spread of ASF within wild boar was simulated by fitting the model to observed data (10). For BTV, the spread in northern Europe has often been modeled using dispersal kernels capturing the vectors being spread in up- and downwind movements (6, 38, 39).

For the current COVID-19 epidemic, several models used to advise the authorities have relied on calibration to hospitalization data rather than the number of test-positive individuals because the latter is known to vary according to changes in testing strategy during the outbreak [https://github.com/laecdtu/C19DK, (13, 14, 40)]. Although this approach is certainly better than the alternatives, it is not without potential pitfalls. During the beginning of the Sars-CoV-2 outbreak in Denmark, substantial technical issues were encountered due to the lack of automated systems for reporting patient numbers. There are also issues around the definitions of "hospitalized due to COVID-19" vs. "hospitalized with COVID-19," i.e., there exists an unknown number of test-positive patients who have been hospitalized for reasons completely separate from Sars-CoV-19 but happen to be concurrently infected—should these be included in the counts? Given the gradual shift in emphasis from targeted testing toward blanket testing of hospitalized patients, this has the potential to introduce a temporally inconsistent bias in the data from the gradual inclusion of more and more "tangential cases" over time. Put together, these issues pose a substantial challenge for the prediction models, which ideally should be mitigated by including more rigorous randomized testing of individuals to provide an unbiased estimate of the proportion of people that have been infected.

Disease spread models are often only verified to the extent of ensuring that the code does what is intended. Validation of disease spread models is quite challenging due to a lack of comprehensive data for validation and impossible in the case of Sars-CoV-2 models for now. Models developed for specific epidemics may be fitted based on the epidemic data. This does not preclude the fact that such models should also be validated, as they include several parameters that are not necessarily obtained from that specific epidemic.

DISEASE MANAGEMENT DURING AN OUTBREAK

In the veterinary field, the success of disease management in case of an outbreak is highly variable depending on several factors, including the extent of disease spread when the disease is discovered; the severity of the disease; the infectiousness of the virus; the density of the population; the speed of application of control measures; the compliance of animal owners; and the involvement of external factors such as vectors, climate, and/or environmental reservoirs. For instance, the 2001 FMD epidemic in the UK took more than a year to control and spread to surrounding countries such as Ireland, Belgium, and the Netherlands (41). Since the introduction of ASF to Europe in 2007, it has been spreading in several parts of the continent as well as in Southeast Asia (8). Recurrent BTV epidemics have occurred in Europe during the past 15 years affecting several countries (42). The control measures that are normally implemented for outbreaks of these diseases (FMD, ASF, and BTV) may vary from one disease to another, but generally, they include a depopulation of the affected herds followed by cleaning and disinfection, surveillance of neighboring herds, and tracing of contacts. Vaccination may be an option when a vaccine is available, as in the case of BTV (43) and FMD (44).

Since the emergence of reports from Wuhan on the spread of a peculiar disease in late 2019 (44), the disease spread to many countries and continents, leading to a pandemic with devastating economic impact (45). In middle March, Europe was declared the epicenter of the disease (46). The management of the disease in Europe varied from one country to another but was characterized by implementing a lockdown, which varied in the speed and degree of its implementation following increase in hospitalization cases. Some countries such as Denmark quickly implemented a partial countrywide lockdown, while Sweden kept several activities running, including schools, restaurants, and bars (47). These diverging strategies have led them along different paths during the epidemic. Testing, contact tracing, and isolation are measures that were recommended by the World Health Organization (48), and peers emphasized the importance of these measures later when the number of cases is low, in order to cut the transmission chain (46).

CONTINGENCY AND PREPAREDNESS PLANS

Detailed and strict guidelines have been set for the control of highly infectious diseases in the veterinary field. For instance, the EU set clear guidelines for the control of FMD, ASF, and BTV in domestic livestock populations (49–51). The member states must follow these guidelines once the disease is detected in the country and demonstrate preparedness and control plans to prevent onward transmission. Furthermore, regular simulation exercises and assessment of logistic and laboratory capacities must be conducted (15, 52, 53).

The current Sars-CoV-19 epidemic has proven the lack of preparedness of many countries to manage a widespread epidemic in human populations (46). For instance, hospitals were not prepared to handle a large number of patients. In addition, some countries, such as Denmark, had no models ready for disease spread in human populations that included the necessary framework to be adjusted to Sars-CoV-19 to advise the authorities from the beginning. Instead, scientists had to build these models within a very short time and develop them as data became available, without following the normal rigor in model development and validation, subjecting the model prediction to high uncertainty. Other countries, such as the UK, adapted an existing model of influenza virus spread (54) to simulate the spread of SARS-CoV-2 and advise the authorities.

DISCUSSION

It seems that ABMs are frequently chosen in the veterinary field to advise the authorities during outbreak situations due to their ability to incorporate a large amount of detail, while different methods are generally used for modeling infectious diseases in humans. Using a farm as the population requires much less computational power compared to modeling all people in a country, which could explain the difference in choice of method. However, because the human population is often more heterogeneously mixed and contains many more behavior patterns than livestock, ABMs would actually be a good choice of model for capturing these patterns (29). Modeling human infectious diseases on a municipality level might be sufficient to capture spatial heterogeneities and provide good tools to advise the authorities on diseases control. However, modeling on smaller aggregations than a country can create problems with parameterization due to fewer cases per subpopulation.

For convenience, some studies have categorized contacts between humans into contacts at home, work, schools, leisure, and others [e.g., 23, 24]. Precise specifications of the contacts are not defined. For instance, who are the receivers of the contacts at home, e.g., other members of the family, friends, neighbors, etc. In addition, the frequency to each of these potential receivers is sometimes not reported. The same issue exists with the other types of contacts. This limits the ability to develop ABM where exact contact structures cannot be simulated, leaving ABMs to be a more or less detailed representation of ODE models. Thus, detailed information on contact structures between individuals is essential to develop reliable predictions from ABMs.

In the veterinary field, experimental studies can be done relatively quickly to obtain necessary data to parametrize models of disease spread. This is a bigger challenge within infectious diseases of humans, as such studies would be unethical. Data sources are therefore typically limited to patients and sometime their contacts, which may include recall or selection bias, so it is highly important to rapidly initiate data collection under ongoing epidemics for the benefit of modeling future epidemics. Specifically, for SARS-CoV-2, it is often reported that cases are most infectious prior to onset of symptoms, so contact tracing of individuals should include repeated testing of contacts to ascertain the shedding of viral loads prior to the onset of symptoms.

From our own long experience in modeling disease spread and control in the veterinary field and the recent experience of modeling SARS-CoV-2 spread in Denmark, we observe that contingency and preparedness planning to handle a highly infectious disease like COVID-19 in humans has been suboptimal compared to similar preparations within the veterinary field. The importance to Denmark of livestock production and exports, including the demands for high-quality products that are made by importing countries, partly explains the importance of contingency and preparedness planning to Denmark. Nevertheless, it is unclear why contingency and preparedness planning for infectious diseases in humans has not so far been done at the same level. One potential explanation is that Denmark (in common with other developed countries) has not experienced a disease as severe as COVID-19 for many years, so contingency and preparedness plans have not been a focus of attention for the health authorities for a disease like COVID-19. We therefore recommend urgent investment in continuous development of contingency plans for human infectious diseases to develop and maintain robust models that can provide accurate predictions in case of a new outbreak with minimized prediction failures. We note that the latter has been a major discussion issue in the current epidemic (55).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TH wrote the first version of the manuscript with assistance from CK. KG, MD, and LC assisted in the writing of the manuscript and provided comments and materials. All authors read and finalized the manuscript.

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Missed Opportunities? Covid-19, Biosecurity and One Health in the United Kingdom

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Whatever we read about Covid-19, the word unprecedented is not far away: whether in describing policy choices, the daily death tolls, the scale of upheaval, or the challenges that await a readjusting world. This paper takes an alternative view: if not unpredictable, the crisis unfolding in the United Kingdom (UK) is not unprecedented. Rather, it is foretold in accounts of successive animal health crises. Social studies of biosecurity and animal disease management provide an "anticipatory logic" - a mirror to the unfolding human catastrophe of Covid-19, providing few surprises. And yet, these accounts appear to be routinely ignored in the narrative of Covid-19. Do social studies of animal disease really have no value when it comes to guiding and assessing responses to Covid-19? To answer this question, we describe the narrative arc of the UK's approach to managing Covid-19. We then overlay findings from social studies of animal disease to reveal the warnings they provided for a pandemic like Covid-19. We conclude by reflecting on the reasons why these studies have been paid minimal attention and the extent to which the failure to learn from these lessons of animal health management signals a failure of the One Health agenda.

Keywords: COVID-19, biosecurity, One health, animal health, social science

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INTRODUCTION: AN UNPRECEDENTED CRISIS?

Unprecedented. Whatever we read about Covid-19, the word unprecedented is not far away: whether in describing policy choices, the daily death tolls, the scale of upheaval, or the challenges that await a readjusting world. This paper takes an alternative view: if not unpredictable, the crisis unfolding in the United Kingdom (UK) is not unprecedented. Rather, it is foretold in accounts of successive animal health crises. In the UK at least, social studies of biosecurity and animal disease management provide an "anticipatory logic" - a mirror to the unfolding human catastrophe of Covid-19, providing few surprises. And yet, these accounts appear to be routinely ignored in the narrative of Covid-19 or as social scientists have sought to claim a place at the disease control table alongside traditional forms of expertise like epidemiology. Do social studies of animal disease really have no value when it comes to guiding and assessing responses to Covid-19? Following Rosenberg's [(1), p. 3] description of epidemics as a "dramaturgic event," we answer this question by firstly describing the narrative arc of the UK's approach to managing Covid-19. We then overlay findings from social studies of animal disease to reveal the warnings they provided for a pandemic like Covid-19. We then reflect on the reasons why these studies have been paid minimal attention and the extent to which the failure to learn from these lessons of animal health management signals a failure of the One Health agenda.

COVID-19 IN THE UK

Rosenburg [(1), p. 2] describes epidemics as a dramaturgic form, following a plot line "of increasing revelatory tension, move to a crisis of individual and collective character, then drift toward closure." In doing so, this narrative arc "illuminat[es] fundamental patterns of social value and institutional practice" (ibid.). The responses to Covid-19 in the UK share Rosenberg's archetypal epidemic plotline: four key stages that are organized around the concept of the "lockdown," the primary strategy adopted by the government to manage the spread of the virus (see **Figure 1**). The acts to this lockdown drama are described below:

Evading Lockdown

For Rosenberg (p. 4), the "progressive revelation" of an epidemic ensures that denial characterizes the first stage of an epidemic: "bodies must accumulate…before officials acknowledge what can no longer be ignored." The UK government's response followed a similar pattern: through late-February and early-March, it came under increasing pressure to act as cases in nearby countries expanded exponentially. The response, released on March 3rd (2), was to evade draconian measures and instead "contain, delay, research, and mitigate." Evasion was based on an understanding of individual rather than collective behavior during emergencies (3). Firstly, the idea of "behavioral fatigue" was used to argue that a lockdown would not be effective because it would be unacceptable to the public, who would become tired of restrictions and behave in potentially hazardous ways (4). Secondly, the idea of "herd immunity" was used in cautioning against a full lock-down. The Prime Minister announced that a balanced approach to protecting the National Health Service (NHS) would mean some people would have to take coronavirus "on the chin." More scientifically, the government's Chief Scientist suggested that herd immunity would broaden and flatten the epidemic peak. Individual responsibility and a sense of duty to "do the right thing" was tasked with defeating Covid-19. Thus, rather than government imposed containment measures, such as banning mass gatherings and closing schools, it was members of the public who took these decisions.

Entering Lockdown

If turning to "rational understanding of phenomenon in terms that promise control," represents the next stage in Rosenberg's plotline (p. 5), this was made palpable in the UK's adoption of lockdown measures by the release of epidemiological modeling in mid-March (5). These models estimated that the containment approach would lead to 250,000 deaths (6). A week later, the lockdown was announced, with policymakers emphasizing that lockdown decisions were reliant on "the science" and the rate of infection (known as the R number). The message to the public was clear: "stay home, protect the NHS, save lives." The approach reflected a dramatic shift away from relying on individual freedom, and highlighted the government's centralized scientific infrastructure involved in controlling disease. Whilst the Scientific Advisory Group for Emergencies (SAGE) and its sub-groups like the Scientific Pandemic Influenza Group on Modeling (SPI-M) had been advising the government since the start, these scientists appeared at daily press briefings, and their advice deferred to in the exclusionary narrative of "the science". Devolved approaches fared less well, reflected in the abandoning of localized test and trace methodologies that had worked well in other countries (6).

Enduring Lockdown

Accompanying this rational understanding, the third act of an epidemic involves routines and rituals and the imposition of "familiar frames of explanation and logically consequent policies" (Rosenberg, p. 7). Throughout the UK's lockdown, a daily government briefing became a scientific stage for "the science" and the "R number" to reassure the public of the government's strategy [cf. (7)]. Targets were set to recruit 18,000 contact tracers, to test 100,000 people a day and to supply millions of pieces of personal protective equipment (PPE). Back-stage the reality was messier with double-counting of tests creating what leading statistician Professor Sir David Spiegelhalter called "pure number theater." If this dented public confidence in the government's handling of the pandemic, it was a mere foretaste. Firstly, a change in messaging from "stay home" to "stay alert" created confusion amongst the public. Secondly, the UK's former chief scientific advisor, David King, established an "Independent SAGE," with a more diverse scientific membership, to address criticisms of the lack of scientific transparency and trustworthiness. Then, news broke that Dominic Cummings - the Prime Minister's chief advisor - and his family had broken rules. Public trust in government plummeted, the devolved governments in Scotland and Wales emphasized their differences, and Cummings was used by the public to justify breaking lockdown rules.

Exiting Lockdown

Whilst epidemics may end with a whimper, their ending also prompts moral judgment: to ask if the "dead have died in vain?" (Rosenberg, p. 9). The ending of the lockdown, began on May 13th, reaching its zenith on "super Saturday" when English pubs reopened on July 4th. Yet this stage is also marked by ambiguity, for example through increasing organizational complexity. This includes the establishment of a Joint Biosecurity Centre, to advise on the UK's coronavirus "alert levels" as part of a new Covid-19 alert system. Chaired by a member of the security services, Covid-19 is reframed as a matter of security and its relationship to existing public health infrastructure is unclear. Organizational complexity is demonstrated too by the reliance on a range of private organizations (such as Serco) to deliver contact tracing or create contact tracing apps. As scientists took a backseat following their daily appearances, politicians took control of the recovery, seeking to "build back better" and restore the economy. The specter of a second-wave, super-spreading events in abattoirs and local lockdowns, suggests the final curtain is yet to fall.

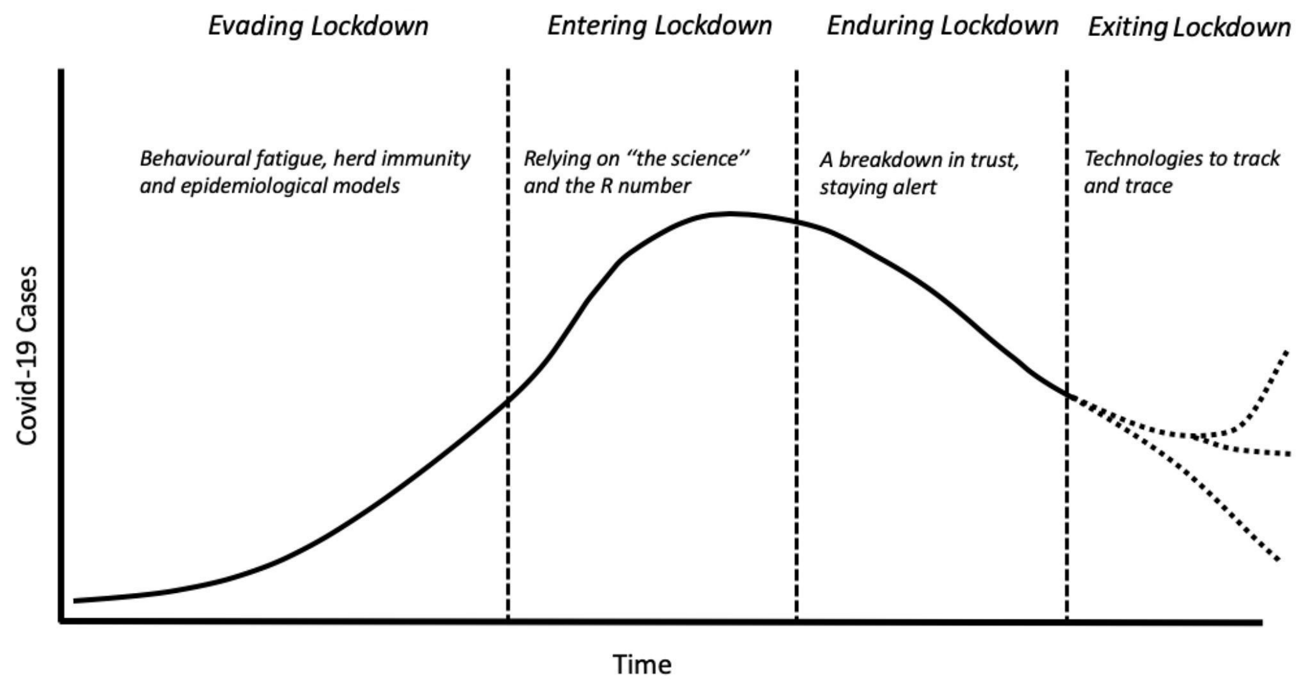

FIGURE 1 | Key stages of the Covid-19 epidemic curve in the UK. Dotted lines reflect the uncertain paths the Covid-19 epidemic may take in future.

THE ANTICIPATORY LOGIC OF ANIMAL HEALTH

If epidemics like Covid-19 follow familiar plotlines, can it be described as unexpected and unprecedented? If the Covid-19 epidemic narrative reflects institutional forms and cultural assumptions, it also reflects how understandings of disease control are too narrowly framed and ignore important lessons from the management of animal disease in the UK over the last 20 years. The outbreak of Foot and Mouth Disease (FMD) in the UK in 2001, for example, focused government attention on preparedness planning, not least because the inability of the government to handle such an outbreak had already been predicted (8). As Anderson (9) argues, "precaution, preemption, and preparedness" have become obsessions, giving rise to "anticipatory logics," and practices of calculating the future to instill resilience across government organizations and responsible conduct amongst the public. Bearing witness to the management of animal disease - its social practices and consequences - can be seen as an anticipatory logic itself. Indeed, as the discourse of "One Health" suggests (10), there should be much to learn and apply from animal to human disease management. For the narrative arc of Covid-19, what would this anticipatory logic have told us, and potentially pre-empted?

Firstly, arguments over the role of epidemiological modeling should be expected because of the way space, subjectivity and politics are encoded within it. The experience of FMD in 2001 highlighted different political choices on which to base decisions. For some, a pre-emptive cull of animals was not only illegal, but socially and economically regressive due to the abstract nature of modeling (11). Other studies of FMD modeling have pointed to the geographical disconnect between computer modelers in distant cities, compared with the situated and nuanced understandings of other experts (such as field veterinarians) whose connection with place provides a different understanding of disease transmission (12). These differences are also tied to spatial styles for governing: command and control is associated with governing from a distance using models that treat space as universal and knowledge as mobile (13). By contrast, devolved approaches are associated with proximate experts and expertise that is situated and variable. Clearly, these distinctions are disciplinary as well as spatial. Thus, different epidemiological subjectivities are endorsed and/or marginalized by choices made by governments when managing disease (14). The management of Covid-19 displays the same pattern: command and control through modeling and the marginalization of local and regional health knowledges. In animal health, the effect of this disciplinary and social marginalization can have long-lasting effects. These studies also point to a better future that recognizes how epidemiological knowledge is not bounded but created in a borderland in which approaches overlap (15) and by integrating participatory forms of modeling (16), more inclusive forms of disease control can be developed.

Secondly, the collapse of trust in the UK government's approach to governing Covid-19 was foretold through the management of animal disease. Starting with Bovine Spongiform Encephalopathy (BSE), government failures in communicating scientific uncertainty (17) have contributed to a lack of public confidence in the handling of disease. BSE was not an isolated incident: the public were similarly alarmed by the handling of

FMD (18), whilst farmers were similarly distrustful of attempts to manage bovine Tuberculosis (bTB). Distrust may stem from the contrast between different forms of understanding disease and the distinctions between scientific and experiential knowledges (19). As Cassidy (20) describes, recourse to "big science" as a means of resolving disputes that rest on values rarely succeeds and often has the opposite effect. Part of the problem here is communicating the distinction between population and individual medicine and the creation of what Rose (21) calls "the prevention paradox." As studies of animal disease show, where population disease interventions fail to correspond to individual experiences, exceptions to the rules, and conflict with cultural norms drives mistrust of government and fatalism. For Covid-19, the reliance on the R number has the same problems. Not only does it misrepresent that epidemics are multiple and vary between sites (e.g. community, hospital and care homes), but the universal presentation fails to reflect how the public have a geographically nuanced understanding of disease risks and transmission (22).

Thirdly, the challenges of creating testing regimes and technologies to track and trace infections are well-understood within studies of animal disease and agriculture. The extent to which testing can deliver on promises set for it will reflect its social organization. For example, in the management of bTB, who conducts tests has come to reflect broad political-economic choices that have infiltrated the management of animal disease. Presumed efficiencies of the private sector have led to the contracting out of disease surveillance but this has not been without consequences. The close "relational distance" between farmers and their own veterinarians paid by government to regulate their clients has raised questions over the "accuracy" of interpretation of test results, as a result of testers acting as field-level epidemiologists and taking local factors into account (23). Similarly, for Covid-19, if test results are to trigger the use and commitment to new track and trace technologies, then these will rely on more than just test results. As Higgins et al. (24) show, acting on biosecurity information involves a different set of behavioral logics than those that are imagined by regulators. The cultural expectation of what counts as "good farming" and the "good farmer" can undermine official guidance on avoiding animal disease or disclosing suspicious symptoms (25, 26). Shaping conduct by governing through individualistic biosecurity subjectivities (27) written into official documents and technologies has limits: use of biosecurity practices and reporting of suspicious deaths and sightings is not simply a matter of "staying alert," but is emergent from a complex relationship of social, economic and environmental relationships (28–31).

Finally, studies of the management of animal disease highlights the mobility of disease experts and expertise. Whilst the psycho-social impacts of eradicating animal disease upon animal disease experts (32, 33) may foretell how medical doctors and health care staff will respond to their own trauma of treating Covid-19, one likely response will be to exit the profession or migrate to other countries as a form of recovery (34). In fact, whilst the UK's initial approach to managing Covid-19 through herd immunity may reflect a form of "British Exceptionalism," animal disease management has recently been anything but international. Policy documents clearly reflect the international spread of logics and technologies of disease management, such as the neoliberal forms of responsibilization and cost-sharing and its technologies of risk-based trading developed in Australia and New Zealand. Nevertheless, whilst the global flow of ideas, experts and expertise appears to continue to shape how disease control is imagined, it is equally true that the globalization of disease regulations has not been met without resistance, as politicians seek to protect their own interests (35, 36). In this sense, in the face of global consensus over the appropriate tools and methods to deploy, the UK's approach finds some precedent in the management of animal disease.

CONCLUSION: WHOSE FAILURE?

In traversing Covid-19's narrative arc, we wish to make three related points. The first is that it seems that social studies of animal disease provide a mirror of clarity to the narrative arc of Covid-19. If paying attention to the management of animal disease provides an "anticipatory logic," it seems to be one worth paying attention to in order to provide the kind of "situational awareness" required to help prevent mistakes from being made in future pandemics. Social studies of animal disease add to the "ecology of knowledges" that are required to resolve problems where "the facts are uncertain, the social stakes are high, decisions are urgent and values are in dispute" - what Funtowicz and Ravetz [(37), p. 744] define as "post-normal science." The warnings and advice that social studies of animal disease can signal may therefore help to broaden institutions "sense-making" capabilities, providing different perspectives and alternatives, and as Weick (38) puts it, to drop familiar tools and develop new ones.

Secondly, there is also a broader lesson for the kinds of social science that can be used here too. One difference between the handling of FMD in 2001 and Covid-19 has been the rise of behavioral science. The pandemic has provided an opportunity for behavioral scientists to reframe disease management as a behavioral problem and claim a place alongside epidemiologists. Their claims of expertise have, however, routinely ignored the social science of animal disease. Thus, Bavel et al. (39) review of the role of social science in managing Covid-19 ignores social research on the human dimensions of managing animal disease. Equally, there is a danger that the social sciences have been narrowly framed: aligned with disciplining the individual perspective of "nudge" behavioral economics rather than acknowledging community action (3). Alternatively, these attempts to provide social scientific certainty, ignore the messy realities of disease and the need to understand the kinds of social work required to make disease control possible (40).

This narrow definition leads to our final question: why have lessons from animal disease studies been ignored? This seems all the more apposite given the extent to which the discourse of "One Health" has become ubiquitous in anticipation of the next pandemic (41). In response to Covid-19, was it most appropriate for veterinary experts to help on the front line of the human medical crisis, donate their PPE from the sidelines, or in the face of a labor crisis, to focus on those dimensions of health (such as veterinary public health) that their specialism allowed? With Chief Veterinary Officers suggesting the latter, the experience of Covid-19 seems to speak to the broader limitations of the One Health movement, or at least, reinforce a demarcation and segregation between its various components. Indeed, social scientific studies of One Health already reveal the extent to which understandings of even an epidemic are socially constructed, distributed and laden with power relations (42, 43). Or, as Hinchliffe [(40), p. 28] suggests, visions of One Health can reduce complexity by focussing narrowly on contamination and transmission, thereby effacing the "local, contingent and practical engagements that make health possible." Rather than this version of One Health, argues Hinchliffe, what is preferable is a version that understands the social work that is required to make health work within increasingly complex disease ecologies. Whilst social studies of animal disease offer an immediate mirror into new and emerging infections like Covid-19, it is toward this longer lasting social understanding of health that might be its greatest contribution.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

GE prepared the main draft. DM contributed material and ideas and edited the text.

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COVID-19 and the Curse of Piecemeal Perspectives

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The world is in turmoil. A novel coronavirus (SARS-CoV-2) has catapulted across the ever-evolving interface between humans and wild places relentlessly spreading coronavirus disease (COVID-19) amongst humans and bringing immense suffering and death to the farthest reaches of our planet. What was immediately apparent was that the virus responsible for this outbreak originated in wild animals. A wildlife source does not come as a surprise as the majority of emerging infectious diseases are zoonotic and two-thirds have their origin in wildlife. The commercial use of wildlife for consumption encompassing both legal and illegal trade is poorly regulated with porous boundaries between the two entities. This trade, particularly in live animals, creates super-interfaces along the food value chain co-mingling species from many different geographies and habitats while creating perfect conditions for the exchange and recombination of viruses. Since the SARS outbreak in 2002/2003, broad scientific consensus exists that long term, structural changes, and wildlife trade and market closures will be required to prevent future epidemics. The pragmatic, most cost-effective action governments can take with immediate effect is to ban the commercial trade of wild birds and mammals for consumption. Most importantly, this reduces the risk of future zoonotic transmission while also safeguarding resources for those Indigenous Peoples and local communities who rely on wild meat to meet their nutritional requirements.

Keywords: COVID-19, SARS-CoV-2, wildlife, trade, market

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INTRODUCTION

The world is in turmoil. A novel coronavirus (SARS-CoV-2) has catapulted across the ever-evolving interface between humans and wildlife relentlessly spreading coronavirus disease (COVID-19) amongst humans and bringing immense suffering and death to the farthest reaches of our planet. Quarantines have been imposed; borders have been closed. Free movement of people and the pursuit of normal daily routines have been dramatically curtailed by a virus that previously existed beyond the pale and a disease that was unknown and unnamed only a few months ago. What was immediately apparent was that the virus responsible for this outbreak originated in wild animals (1). A wildlife source does not come as a surprise as the majority of emerging infectious diseases are zoonotic. Globally, more than 335 Emerging Infectious Disease (EID) outbreaks, involving 183 distinct pathogens, were reported between 1940 and 2004 (2). That's more than 50 outbreaks per decade, and the rate is increasing. More than half (52%) of all EID events in recent years originated in wildlife (2). Among emerging zoonoses specifically, 72% of outbreaks have originated in wildlife with the rest emerging from domestic animals (2). Emerging zoonoses have significant implications for both public health and economic stability with the costs of many individual recent major outbreaks such as SARS, MERS and Ebola estimated in the tens of billions of US dollars. These costs exceed 1–2% of GDP in less wealthy countries and surpass the International Monetary Fund's threshold (0.5% GDP loss) for major economic disasters (3). When all is tallied, it is certain that the economic devastation caused by COVID-19 will be orders of magnitude greater: in the trillions to tens of trillions of US dollars.

WHAT DO WE KNOW?

As in previous zoonotic coronavirus spillover events of global concern, a bat species is most likely the evolutionary host to the on-going SARS-CoV-2 pandemic (4). Initially, in December 2019, human cases, were epidemiologically linked to a seafood market in Wuhan, China, where live wild animals were sold and slaughtered for consumption (5). However, not all of the first human cases were market associated. To date, timing, location and mechanisms of the spillover event(s) have not been conclusively determined and possibly will never be due to the apparent lack of animal sampling in the early days of the outbreak (5). All three zoonotic-origin coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) result from recombination. Ancestral and recent viral recombination events between bats, pangolins, and still to-be-identified additional hosts most likely made it possible for SARS-CoV-2 to acquire the attributes necessary to infect human cells and subsequently transmit from humans to humans (6).

THE WILDLIFE TRADE FOR CONSUMPTION

While robust data is lacking, the legal and illegal trade in wildlife is valued at hundreds of billions in US dollars (7). Wildlife trade is driving species extinctions and is a critical factor in global biodiversity loss (8). The illegal trade in wildlife is the fourth most profitable crime after drugs, human trafficking, and arms and generates at least USD 23 billion in illicit annual revenue (9). Data on the value of the global commercial wildlife trade for consumption is sparse, but the global total annual value of wildlife harvesting is estimated at USD 400 billion (10). This sum includes household community-based hunting for subsistence consumption and surplus sale, but a far greater proportion reflects community-external hunting that supply national and international trade (10). It is thought that there are some 20,000 wildlife farms, employing more than 6 million people and generating an estimated USD 18 billion dollars in China alone (11). Across southern Viet Nam, 4,099 active farming operations, stocking an estimated one million wild animals (including, rodents, primates, civets, wild boar, Oriental rat-snakes, deer, crocodiles, and softshell turtles). were recorded (12). These farming operations supply wild animals predominantly for meat for human consumption and sell to national urban wild meat restaurants that serve increasingly affluent populations. They simultaneously supply international markets with wild meat (13). The commercial use of wildlife for consumption encompasses both legal and illegal trade that is poorly regulated with porous boundaries between the two entities [e.g., (14)]. The trade involves the capture, transport, and containment of wild animals. These activities induce stress, injury, sickness, and compromise immune systems. The multiple stressors inhibit animal immune responses and allow for enhanced shedding of pathogens (15). Stress also leads to increased excretion of saliva and voiding of urine and feces, all of which facilitate the shedding of viruses.

Genetic change in viruses is driven by several mechanisms, amongst them recombination, which occurs when two or more viral genomes co-infect the same host cell and can exchange genetic segments (16). This trade, particularly in live animals, creates super-interfaces along the food value chain co-mingling species from many different geographies and habitats (that would never have otherwise come into contact). A recent study from Vietnam demonstrated that the odds of coronavirus RNA detection among field rats (*Rattus* sp. and *Bandicota* sp.) destined for consumption increased significantly along the supply chain from traders to markets to restaurants (17). Wildlife trading sites, as in the Wuhan market, are vast, industrialized centers, cramming thousands of live animals from hundreds of species alongside thousands of domestic animals. This contrasts starkly with small stalls where local communities exchange and sell wildlife for subsistence. Furthermore, not only do animals exchange viruses among themselves, but vendors and customers also circulate within this milieu while slaughter and purchasing practices continually generate potential spillover opportunities. The commercial live wildlife trade and wildlife markets constitute true caldrons of contagion.

WHAT NEEDS TO BE DONE IN THE FUTURE?

First and foremost, we must acknowledge the basic tenet addressed by World Health Organization (WHO) Director-General Dr. Tedros Adhanom Ghebreyesus: "*The pandemic is a reminder of the intimate and delicate relationship between people and planet. Any efforts to make our world safer are doomed to fail unless they address the critical interface between people and pathogens, and the existential threat of climate change, that is making our Earth less habitable*"(18). We also have to acknowledge that zoonotic spillover events and subsequent outbreaks are inevitable, as the interfaces between wildlife and humans increase, primarily due to deforestation and agricultural expansion (19). However, our collective and determined actions can prevent outbreaks from becoming global pandemics. Reducing spillover opportunities necessitates multi-faceted approaches that include amongst others, considering wildlife pathogen impacts during land-use change, social marketing campaigns to reduce wildlife demand, providing alternative protein and micro-nutrient sources, strengthen law enforcement response to illegal wildlife trade. While much insight has been gained in the past decade, in part due to large research consortiums such as the USAID-funded PREDICT projects, there are still substantial gaps in knowledge concerning, amongst others, viral threats and spillover mechanisms. Future multidisciplinary and well-funded collaborative One Health approaches are urgently needed to quantify and prioritize spillover risks while informing decision-makers on implementing risk reduction measures. Pre-emergence research and surveillance need to be paired with participatory, just and community-informed social and behavioral change measures and global outbreak preparedness capacity strengthening.

WHAT NEEDS TO BE DONE NOW?

The pragmatic, most cost-effective action governments can take with immediate effect is to ban the commercial trade of wild birds and mammals for consumption. Most importantly, this significantly reduces the risk of future zoonotic transmission while also safeguarding resources for those Indigenous Peoples and local communities (IPLCs) who rely on such. Furthermore, it protects global biodiversity (20). This expedient and straightforward risk mitigation measure is surprisingly contentious in the public arena. Four unsound and inconsistent approaches are presently being widely promoted in the media, and to governments and donor institutions: (i) The sole focus on markets is inherently flawed as markets constitute just one part of the wildlife trade supply chain. Along the supply chain, multiple points pose a high risk of zoonotic pathogen transmission, including wholesale trader warehouses, stores, transport, wildlife farms, restaurants, pet shops, and border crossing points where wildlife is consolidated (18, 21); (ii) Similarly, vocal advocacy for closure of only the (as yet undefined) 50 highest-risk markets represents a dangerously unsound approach (22) that discounts the magnitude of the problem: Following China's Standing Committee of the National People's Congress decision to eliminate the consumption of wild animals for food to safeguard people's lives and health on the 24 February 2020, the National Forestry and Grassland Administration confiscated 39,000 wild animals and "cleaned up" more than 350,000 sites, such as restaurants and markets where wildlife was traded. Additionally, some 17,000 online accounts and e-commerce platforms trading wildlife products were closed down. Closing 50 markets appears frivolous at best (23); (iii) The focus on so-called high-risk species lacks evidence and defies enforcement. Numerically abundant orders such as rodents and bats harbor more viruses, but the notion of "special viral reservoirs" has recently been revoked (24). Most pathogens in wildlife remain unidentified, and many spillover events are overlooked (19). Less than 300 viruses from 25 high-risk viral families in mammals and birds are known to infect people. Yet, it is estimated that there are around 1.7 million viruses from these same viral families that have not yet been discovered. About 700,000 are predicted to have zoonotic potential (25); (iv) Enforcing hygienic standards, sanitizing markets and restaurants that sell wildlife is similarly being heavily promoted by numerous wildlife trade-related organizations (22, 26). There is ample evidence, especially from the avian influenza literature, that hygiene and management measures cannot prevent the resurgence of outbreaks (27).

DISCUSSION

Since the SARS outbreak in 2002/2003, broad scientific consensus exists that long term, structural changes, and wildlife trade and market closures will be required to prevent future epidemics (6, 28, 29). This mode of action is now also supported by intergovernmental organizations, such as the WHO, and international legal instruments, such as the Convention on Biological Diversity (29). In contrast to what some authors have suggested, no one, to my knowledge, is under the impression that closing down the global commercial trade of wildlife for human consumption is simple or that this is the only measure that needs to be addressed. Playing one necessary measure against another, confusing Central Africa with the situation in South-East Asia and China is simplistic and negligent (30). Based on the robust scientific evidence available, we must stridently reject assertions that cultural importance and the economic value of commercial wildlife meat retail, outweigh a devastating global pandemic that has impacted the entire planet, caused hundreds of thousands of deaths and cost the global economy USD trillions. Ostensibly raising concern for food security of IPLCs is a thinly veiled smokescreen to enable a return to business as normal while distracting from the fact that large, live-wildlife-trading markets in South-East Asia and China predominantly cater to the economically empowered middle and upper classes supplying expensive wild luxury meats and ego-bolstering status symbols. Food security and rights of IPLCs do not rely on international trade in live wildlife. On the contrary, this unsustainable, profit-oriented trade empties the forests of the very wildlife the IPLCs depend on (31). Furthermore, it has been estimated that the COVID-19 pandemic will add somewhere between 83-132 million people to the total number of undernourished people on this planet (32). Most importantly, rejecting scientific evidence paired with unclear and myopic messaging undermines the progress being made in key wildlife trade countries. In China, law-makers in the National People's Congress are moving toward legislating the February Decision to prohibit the trade of wild animals for human consumption. In Vietnam, following the announcement in March 2020 by the Prime Minister Nguyen Xuan Phuc to "take strong and sustainable actions to halt all illegal wildlife trade and consumption in Vietnam," a new taskforce committed to reforming policies to prohibit the commercial trade and consumption of wild birds and mammals has launched into action. While these legislative actions are to be commended, it is essential to pair these with pervasive educational and social marketing measures to drive change across civil societies concerning wildlife usage. For preventive measures to persist in the long term, global funding support is required. Recently, these global preventive costs for 10 years are estimated at 2% of the costs of the COVID-19 pandemic (33).

The increasing incidence of viral spillover events is a symptom of ailing planetary health. As human activities and encroachment increasingly undermine the integrity of naturally balanced ecosystems, environmental health, and resilience are compromised affecting all species on the planet. Spillover events reflect impact not just on human health but the health of all the earth's organisms. Viral, species switching, and spillover events into humans are simple. It all comes down to a numbers game: the more often we force conditions that drive increases in direct contacts of wildlife and humans, the higher the likelihood of another spillover event. Timidly tackling a limited number of markets and developing standards that purportedly regulate and sanitize wildlife trade are backward-looking reductionist approaches based on naïve simplifications of interdependencies in disease emergence, economic development, and global interconnectedness.

The time has come for the global community to collectively assume responsibility for the negative externalities of the commercial trade in wildlife for consumption. The world has irrevocably changed and there can be no going back. As we, the global community, strive to build back better, we must ensure that future food production and security is healthy, sustainable and supports planetary health. A transition of global food production from being a major part of the health, climate and biodiversity crisis toward food production playing a central part in the solutions. We need bold, forward-reasoning organizations and leaders who acknowledge root causes, take responsibility and weather the inevitable pushback from narrowly focused interest groups while also overcoming traditional economic and disciplinary silos to design future health and well-being for all.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CW conceived, developed, researched, and wrote the manuscript.

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PERSPECTIVE
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Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2): A Perspective Through the Lens of the Veterinary Diagnostic Laboratory

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The SARS-CoV-2 pandemic has resulted in unprecedented challenges to veterinary diagnostic laboratories. These challenges include partial or complete shutdowns, interrupted courier services, disruptions in workflow and diagnostic testing, new physical distancing practices, protocol development or enhancement for handling samples from high-risk or susceptible species, and fulfilling requirements for pre-test permission approval from state and federal veterinary agencies, all of which have been implemented to prevent or minimize exposure and transmission of SARS-CoV-2 locally or regionally. As in people, SARS-CoV-2 infects animals through direct animal-to-animal contact and aerosol transmission between animals. Humans can also infect pets or other animals in their care and, although human-to-human transmission is the main route of viral spread in people, infected animals and specimens of their bodily fluids or tissues are a potential source of infection for veterinarians and technical or laboratory personnel that are handling them. In this perspective, we discuss how SARS-CoV-2 has necessitated rapid changes in laboratory operation to minimize zoonotic risk to personnel and to implement tests for identifying the virus in animals. The pandemic has highlighted the adaptability and quick response of veterinary diagnosticians to an emerging infectious disease and their critical role in maintaining animal health, while synergizing with and protecting human public health.

Keywords: COVID-19, diagnostic testing, serology, molecular genetics, viral infection, wildlife, zoological animals, public safety

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INTRODUCTION

A once in a lifetime global pandemic due to SARS-CoV-2 is upon us and veterinarians are rising to the challenge, responding quickly to this novel zoonotic disease. Veterinarians are trained in comparative medicine across species and to always consider infectious diseases when examining or treating animals or handling bodily fluids and tissues for diagnostic testing. As such, veterinarians have the expertise to contribute to discussions and research related to disease pathogenesis as well as to concerns of disease transmission from animals-to-humans and humans-to-animals, with the attending health implications for animals. For veterinary pathologists and diagnosticians, the outbreak has necessitated rapid implementation of molecular and serologic assays as screening, diagnostic and research tools for SARS-CoV-2, enhancement of protocols to ensure safety of laboratory personnel handling fluids and tissue from susceptible, suspect, or infected animals, and reconfiguration of laboratory spaces with modification of procedures to facilitate operation while maintaining local, regional, and national guidelines for personal protection, including physical distancing.

Veterinary diagnostic laboratories are adept at analyzing many different specimens from a wide array of species using standard operating procedures, akin to those in human medical laboratories. These procedures include mandatory personal protective equipment (PPE), such as gloves and dedicated clothing, and engineering controls that vary depending on the biosafety level (BSL) concern and risk assessment. Laboratories are also well-equipped to handle samples that may have come from an animal infected with an organism of high zoonotic potential, such as cerebrospinal fluid (e.g., rabies), blood and tissue (e.g., anthrax), and urine (e.g., leptospirosis). SARS-CoV-2 is a new addition to this existing list of zoonotic diseases that pose a risk to laboratory personnel, although cases of laboratory-acquired SARS-CoV-1 infections are rare in human medicine (1, 2) with none-to-date reported for SARS-CoV-2 in human or veterinary diagnostic laboratories. Nevertheless, given the frequently unknown infectious status of animals or their owners, veterinary diagnostic laboratories have re-evaluated protocols to further reduce risk to personnel handling samples, particularly from species susceptible to SARS-CoV-2.

SUSCEPTIBLE ANIMAL SPECIES

Domestic and non-domestic felids, dogs, ferrets, mink, non-human primates, and hamsters can be naturally or experimentally infected with the virus, with shedding of variable degree and duration and evidence of inter-individual transmission (3–19). Subsequent to the original animal-to-human transmission event and resulting human-to-human transmission, the current infection paradigm is that companion and non-domestic farmed or captive animals acquire the virus from humans. However, the infection rate in pet animals appears low. In a study from Italy, viral RNA was not detected in nasopharyngeal, nasal and/or rectal swabs from 839 pet dogs and cats, including 76 animals with clinical signs of respiratory disease. Of the tested animals, 14% were from households with COVID-19 (20). Serum neutralizing antibodies was detected in 3–4% of animals, although a higher proportion of serologically-positive dogs were from COVID-19 vs. non-COVID-19 households. In two other studies of 21 (dogs and cats) and 23 (dogs, cats, rabbits, and a guinea pig) pet animals from France (21) and Spain (22), viral RNA was detected in a nasopharyngeal swab from one cat in the Spanish study (22). In contrast, 15% of 143 pet and stray domestic cats had serum antibodies to SARS-CoV-2 in a study conducted in Wuhan, China, after the outbreak; cats with the highest titers were from households with COVID-19 (23). It is unclear if these differences relate to actual exposure or variability in performance of the applied tests. To date, there has only been one report of suspected animal-to-human transmission from farmed mink (24), suggesting that zoonotic transmission to people is still possible when working with high numbers of susceptible animals in close confined quarters. Based on gene sequencing, the ancestral SARS-CoV-2 virus is thought to have its origin in a species of bat with subsequent evolution to its current form in one or more intermediate animal hosts, possibly including pangolins (25, 26). The spike protein on the virus envelope facilitates cell entry by binding to the transmembrane protein, angiotensin-converting enzyme-2 (ACE2). Amino acid sequencing of the spike protein binding domain and ACE2 and *in silico* modeling of the spike protein binding to ACE2, is being used to explore susceptibility of experimental and domestic animals to SARS-CoV-2 and identify potential wildlife hosts (6, 27–30). Two modeling studies predict that equine, camelid, bovine and ovine ACE2 will bind SARS-CoV-2 (27, 30), however no infectivity studies have been reported as yet for these species. Similarly, *in vitro* studies of the spike protein (in pseudotyped virions) binding to cloned ACE2 and infection studies of cell lines derived from different species suggest that rabbits may be infected with the virus (31, 32). However, as shown for pigs (12, 33), modeling and *in vitro* studies do not always translate into susceptibility *in vivo*.

LABORATORY HANDLING OF SPECIMENS THAT MAY CONTAIN SARS-CoV-2

Specimens with the highest biohazardous risk to laboratory personnel are respiratory secretions and tissues that contain infectious virus (5–10, 12, 16, 19, 34–37). Direct mucosal contact with or inhalation of respiratory droplets or aerosols are the primary routes of infection (9, 19, 38), with intranasal administration being the experimentally used counterpart of natural infection (6, 7, 9, 10, 12, 19, 34, 37, 39). A brief low-level viremia has been documented in several human patients (40–43) and experimentally infected ferrets (9), macaques (10), and hamsters (6). In humans, viral RNA can be found in feces and rarely in urine (36, 41, 43, 44), with one report of infectious virus in feces (45). Viral RNA has been amplified from feces in domestic and wild felidae (12, 16), feces and urine from ferrets (9) and feces from monkeys (46), with infectious virus being isolated from feces from non-domestic cats (16), ferrets (9), and monkeys (46). While feces, urine and blood may not contain as much intact virus as respiratory samples, they are still considered infectious, but likely pose a low risk to laboratory personnel. Longitudinal studies of the infectious nature of respiratory secretions, other bodily fluids, such as saliva, and feces or rectal/anal tissue are needed across a range of domestic and non-domestic animals and livestock to develop a clear understanding of the relative risk and the duration of risk that these biomaterials pose to owners, laboratory personnel, and contact animals.

When handling samples from SARS-CoV-2 susceptible animals for routine laboratory testing, guidelines established by government entities are followed [e.g., Centers for Disease Control and Prevention (47) and Public Health England Gov. UK. (48)]. These guidelines recommend standard protocols, with additional precautions for higher risk procedures that can generate aerosols, such as centrifugation or autopsies. Veterinary laboratories typically operate under BSL-2 conditions (49), with most samples for microbiological or molecular diagnostic procedures being handled within a microbiological or biological safety cabinet (BSC). Inactivation steps are often included in protocols, but are not always feasible or desirable. For cytologic samples, optimal preparation of tracheal wash and bronchoalveolar lavage fluids often requires centrifugation-based concentration. Additional protective measures for handling such specimens could include face protection for benchwork, using BSC for preparing slides, only preparing direct smears for examination (feasible for tracheal washes but not low cellularity bronchoalveolar lavages), using centrifuges with sealed rotors (cytocentrifuges), operation of or opening centrifuges within BSC, and alcohol- or heat-fixing slides (which may adversely affect smear quality). Smears of respiratory secretions on unstained unfixed glass slides may contain live virus for several hours to perhaps days (50, 51), however, virus is unlikely to be aerosolized from the slides and unstained/unfixed slides pose low risk if handled with appropriate PPE. It is assumed slide staining, particularly with alcoholic-based stains, will inactivate virus, but this theory remains to be tested. Recommendations for autopsies on suspect COVID-19 human patients include N95 masks, eye protection, conducting minimally invasive autopsies (e.g., ultrasound-guided needle biopsies), and delaying autopsies until confirmatory testing is complete (52). Similar recommendations have not been published for post-mortem examination of animals, however existing protocols for highly pathogenic zoonotic diseases can be modified to include targeted sample collection for SARS-CoV-2 in suspect cases with approval (53, 54) and guidance on collection (47, 48, 55, 56).

TESTING FOR SARS-CoV-2 IN LABORATORY SAMPLES FOR ANIMALS

Veterinary diagnostic laboratories play an essential role in disease outbreaks through testing for the organism and antiviral immunity and through educating clients about the relevance of positive and negative results. Testing is the core of epidemiologic studies of prevalence and spread, associating infection with disease, and identifying susceptible hosts or vectors. Local, state, national, commercial, academic, and research veterinary laboratories quickly adapted existing methods and validated tests to identify SARS-CoV-2 RNA or antigen and serologic responses in animals. In the early pandemic phase, several veterinary laboratories were approved for SARS-CoV-2 testing on human samples in the event that expanded capacity was needed by the human health community (57, 58). Currently, 9 of the 59 veterinary diagnostic laboratories within the National Animal Health Laboratory Network (NAHLN) have been certified by the Department of Health and Human Services to perform testing of human samples in the United States (59), demonstrating how readily veterinary laboratories can be repurposed at times of need. Many laboratories donated equipment, reagents, and supplies as part of their pandemic efforts.

The current standard for detecting active SARS-CoV-2 infection and determining infection prevalence is through real time reverse transcriptase-polymerase chain reaction (rRT-PCR) for SARS-CoV-2 RNA. The test is exquisitely sensitive and specific. However, care must be taken to correctly interpret results and avoid false positive or negative results. False positive results can occur through cross-sample contamination during collection or testing (60–62). Confirmatory testing, ideally from a different laboratory, would increase confidence in positive results. A positive rRT-PCR reaction does not necessarily indicate replication-competent virus and an infectious patient, since degraded RNA may be detected (60). Virus isolation can verify that RNA equates to infectious virus in natural and experimental infections, but requires BSL-3 facilities and suitable cell lines for infection (e.g., Vero cells). False negative rRT-PCR results can be due to patient factors (e.g., intermittent shedding), sample collection (e.g., wrong timing, insufficient or inadequate specimens), sample handling (e.g., RNA degradation with storage), or test limitations (e.g., inadequate RNA extraction, insensitive primers, RNA levels below detection limits in early or low-level infections) (60–62). Viral RNA can be detected *in situ* using RNA hybridization and virus-specific probes in research studies (7, 10, 11, 16, 42). As for any laboratory test, it is critically important to include positive and negative controls and verify specificity for SARS-CoV-2 to prevent cross-reaction with other coronaviruses, minimize the likelihood of false positive or negative reactions and verify test performance.

Immunologic-based tests are used to detect SARS-CoV-2 viral antigen or antibodies indicative of a serologic response to infection. Immunohistochemical application of monoclonal or polyclonal antibodies against the spike and nucleocapsid proteins has been invaluable for determining viral tissue tropism in experimental studies (5, 6, 8, 9, 11, 34, 39, 42). However, the presence of viral antigen in bodily fluids does not necessarily indicate infectious virus, because antibodies can bind to inactivated virus, such as in formalin- or alcohol-fixed samples. Serologic assays for anti-SARS-CoV-2 antibodies can be performed with ELISA, multiplex assays or other platforms, including those designed for point-of-care use. However, a positive reaction does not necessarily equate to immunity and, like any diagnostic test, false positive and negative reactions occur, with a higher likelihood of false positive reactions in regions with low prevalence. In veterinary settings, the lack of species-specific secondary antibodies can be a major limitation for serologic testing. Thus, serum neutralization assays are often used to detect antibodies, especially when testing samples from non-domestic wildlife or zoological animals (16). Antibodies for immunologic testing should be thoroughly validated, as described for immunohistochemical staining (63). The sensitivity and specificity of immunologic-based tests depends on antibody avidity, the antigenic epitopes detected by the antibodies, and detection method; different assays may not yield equivalent results. For example, a recent meta-analysis comparing performance of serologic SARS-CoV-2 assays in human patients showed that fluorescence- or point-of-care chromatographic-based assays were less sensitive than ELISA- or chemiluminescence-based assays and ELISAs targeting the spike protein were more sensitive (albeit with overlapping confidence intervals) than those against the nucleocapsid protein (64). Larger scale studies to evaluate assays across platforms are underway in human medicine and are yet to be done for animal testing. Veterinary diagnostic laboratories have a wealth of archived and fresh samples from multiple species to use for test validation and determining repeatability and performance of currently used and newly developed assays. One program to verify performance across veterinary diagnostic laboratories (Inter-Laboratory Comparison Evaluation) is being established by the United States Food and Drug Administration's Veterinary Laboratory Investigation and Response Network on behalf of the NAHLN (Dr. François Elvinger, personal communication). Recognizing the need for the rapid development of SARS-CoV-2 tests, future goals should include independent assessment of test performance to support developers' claims of sensitivity and specificity, testing for inter-laboratory agreement, production of high-quality control materials for internal and external proficiency testing, and open-access publication or reporting of methods and test performance statistics. Such studies and transparency are necessary to inform clients and the public of test performance and increase confidence in test results, whether performed in diagnostic laboratories or at point-of-care.

DISCUSSION

SARS-CoV-2 is a new addition to the list of zoonotic agents that might be present in animal specimens handled and tested in veterinary diagnostic laboratories. Procedures that were rapidly put in place in an emergent situation to deal with high-risk samples will need to be revisited and refined as more information about the virus comes to light. No doubt the virus will be a hot topic of conversation at future pathology and diagnostic association scientific meetings, where shared experiences, successes, and failures will help inform policy and protocols. Ideally, these discussions will lead to the development and adoption of industry-wide or consensus standards for sample handling and testing, result reporting and interpretation, and archiving and disposal of high-risk specimens. It is also likely that the list of susceptible animal species will continue to grow as additional natural infections are identified and knowledge is acquired from research studies on domestic, wild, and zoological animals. Many questions about the virus remain to be answered, such as how long the virus persists in laboratory samples, how best to inactivate the virus in routine preparations (e.g., smears of potentially infected material on glass slides) while maintaining diagnostic quality, and whether routine staining of such slides inactivates the virus. Veterinary diagnosticians and researchers are well-poised to take advantage of their substantial available resources to perform these studies.

In the United States, routine SARS-CoV-2 testing is currently not recommended in animals (53, 54, 65). Arguments against widespread testing include the lack of understanding of the meaning of positive or negative results, lack of clarity on appropriate preventative or therapeutic interventions for animals with positive results, and concerns for animal and human welfare, such as pet abandonment or euthanasia, killing of wildlife populations, and disruption of the human-animal bond when separating owners from pets. In the early days of the pandemic, there was negative public perception for testing animals when human facilities needed reagents and supplies for testing people. Current animal testing guidelines recommend first ruling out other conditions, justification of need, and approval by state veterinarian or public health officials, with confirmation of presumptive positive results by the National Veterinary Services Laboratory in Iowa (53). The World Organization of Animal Health has defined SARS-CoV-2 as a reportable emerging disease (66). However, the situation is rapidly evolving and there remains a need to better understand the true prevalence of SARS-CoV-2 in companion, working or food animals, and zoological and wildlife populations, which can be accomplished by studies involving broader testing. Improved knowledge of true prevalence would better inform veterinary clinical and laboratory practice and owners of such animals, enabling science-based recommendations for risk assessments. More testing will also allow us to refine our understanding of virus epidemiology and establish whether and which animals are reservoirs of the virus, information critical to break transmission chains and protect animal and human health. SARS-CoV-2 testing in animals is generally performed on nasopharyngeal swabs, fecal samples or rectal swabs (3, 5, 7–10, 12, 16, 19); testing on saliva may be an additional option in animals (9, 35). Fecal sampling is an appealing non-invasive collection method, allowing ready surveillance of at-risk wildlife or zoological animals, albeit at the risk of reduced sensitivity due to less viral RNA (16). Shedding periods may extend beyond the period of clinical signs, thus fecal testing may help us understand how long shedding persists, which will contribute to risk assessments and epidemiological investigations into transmission.

The mission of many veterinary diagnostic laboratories includes the provision of diagnostic testing for disease identification and maintenance of animal health, food security, and human public health. Sustaining efficient ongoing operations is essential to allow veterinary diagnostic laboratories to continue to fulfill this mission. The current pandemic complicates delivery of this mission, however veterinary laboratories have shown remarkable adaptability and innovation when handling this unprecedented crisis. At least in the near term, and potentially until effective vaccine(s) are available, some laboratories may institute regular testing of personnel to minimize the likelihood of localized outbreaks among staff and prevent major disruptions in laboratory services. The pandemic also offers a rich opportunity for veterinary diagnosticians and pathologists to contribute to testing and research, through primary or collaborative efforts.

Veterinary diagnostic laboratories have responded to the call of the SARS-CoV-2 pandemic by rapidly establishing new or enhancing existing protocols to ensure safe laboratory practices and implementing and validating molecular- and immunologic-based assays for virus detection. They have also helped to expand testing capacity for human patients, all while concurrently performing routine diagnostic testing for other animal diseases and often with reduced staffing related to governmental or organizational mandates. The combined expertise of anatomic and clinical pathologists, molecular diagnosticians, and virologists, working collaboratively as teams with highly qualified and dedicated personnel, positions veterinarians to be key partners in understanding natural disease that impacts human health, such as this coronavirus pandemic, as well as for leading or collaborating with discovery efforts into viral pathogenesis, diagnostic testing, and treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

TS wrote the article, which was edited by DM, KT, and FS. All authors contributed to the article and approved the submitted version.

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REVIEW
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COVID-19 Effects on Livestock Production: A One Welfare Issue

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The COVID-19 pandemic highlights that we exist in a global community. From a single city, it spread to 188 countries across the world and infected 30 million people by September 18, 2020. Decades of modeling pandemics predicted potential consequences, but COVID-19's impact on the food supply chain, and specifically livestock production was unexpected. Clusters of cases among workers in meat processing plants evolved quickly to affect human, animal, and environmental welfare in several countries. In processing plants, the hygiene focus is on product quality and food safety. Because of their close proximity to one another, COVID-19 spread rapidly between workers and the lack of sick leave and health insurance likely resulted in workers continuing to work when infectious. In the United States (U.S.) many processing plants shut down when they identified major outbreaks, putting pressure especially on pig and poultry industries. At one point, there was a 45% reduction in pig processing capacity meaning about 250,000 pigs per day were not slaughtered. This resulted in longer transport distances to plants in operation with extra capacity, but also to crowding of animals on farm. Producers were encouraged to slow growth rates, but some had to cull animals on farm in ways that likely included suffering and caused considerable upset to owners and workers. Carcass disposal was also associated with potential biosecurity risks and detrimental effects on the environment. Hence, this is a One Welfare issue, affecting human, animal, and environmental welfare and highlighting the fragility of intensive, high-throughput livestock production systems. This model needs to be re-shaped to include the animal, human, and environmental elements across the farm to fork chain. Such a One Welfare approach will ensure that food production systems are resilient, flexible, and fair in the face of future challenges.

Keywords: poultry, pigs, livestock production chain, one welfare, COVID-19

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INTRODUCTION

The emergence of a novel pandemic disease should not have taken the world by surprise. Within the last century, the 1918 influenza pandemic infected an estimated 500 million people and killed 17–50 million (1). More recently, the 2009 swine flu pandemic infected about 61 million and killed an estimated 284,000 (2). Both pandemics were H1N1 influenza viral diseases and it is perhaps natural that the focus for predicting future pandemics was on influenza, with a Web of Science search for "pandemic AND prediction" showing that 290 out of 415 articles since 2010 include "influenza" [e.g., (3)] whereas only 15 include "coronavirus" [e.g., (4)]. However, recent SARS and MERS outbreaks showed that coronaviruses are strong candidates for zoonotic pathogen spillover

(5). This is combined with the threat of zoonoses emerging from wild animal populations, especially in regions of the world where wildlife biodiversity is high and land-use change is occurring (6). This is against a background of pressures arising from climate change, food security, and safety (7) and antimicrobial use and resistance (8).

After the swine flu pandemic, the World Health Organization conducted a review of its first line of defense—its International Health Regulations (2005)—and concluded that, "The world is ill-prepared to respond to a. . . global, sustained and threatening public-health emergency." (9). Until now, the major perceived threats in intensive livestock production were a pandemic outbreak of a foreign animal viral disease, exacerbated by secondary bacterial infections and potential concurrent antimicrobial resistance driven by use of medically important antimicrobials. A pandemic may bring expected challenges but there are always unforeseen ramifications that transcend human health (10). The interconnectivity of human health with that of animals and the environment is captured in the One Health concept, which is defined as "the collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals, and our environment" (11). The concept of One Welfare extends One Health to recognize "the interconnections between animal welfare, human well-being and the environment" (12). This paper will focus on the impact that COVID-19 is having on One Welfare within livestock production from farm to fork with particular focus on the pig and poultry industries. We focus on the United States (U.S.) as it is one of the hardest hit countries so far where related data are readily available and accessible. However, we expect that the situation is similar in all affected countries with intensive livestock production industries.

COVID-19 EFFECTS ON THE LIVESTOCK PRODUCT SUPPLY CHAIN

Livestock, and particularly pig and poultry, production in the industrialized world, and increasingly in the developing world, is characterized by its intensive nature, initially driven by post-war government policies intended to increase production and decrease cost, but now sustained by consumer demand for cheap food (13). Farms are fewer in number but larger, with more animals and birds per holding in enclosed, climate-controlled buildings, with more automation and fewer stockpersons. Vertical integration is common, meaning a single company will own all parts of the system, from feed mill to processing plant. The production system is primed for maximum output, with all parts of the chain from birth/hatch to slaughter always operating at full capacity. Disruption of flow at any part of the chain will therefore have immediate impact both upstream and downstream, with likely immediate consequences for animal welfare but also for humans and the environment. The immediate impact of COVID-19 was a wave of panic buying by the public. Among the products to disappear from supermarket shelves in the first few days were toilet rolls, disinfectants and sanitizers, pasta, rice, flour, and yeast, and in some countries, eggs, cheese, and milk. General trends included increased meat, egg, and dairy retail sales with a sharp upward spike as lockdowns were announced (14), but then sustained sales when compared with year-on-year, from early March to July, where records are available (15). This was a consequence of the increase in meals being prepared at home, with schools, workplaces, and restaurants closed.

Countries such as the U.S. have two relatively distinct supply chains: one that supplies grocery stores and one that supplies the food service industry. Hence, gaps on shelves did not represent a shortage of commodity *per se* but the commodity existing in forms unsuitable for supermarkets compounded by distribution chains unable to cope with increased retail demand. As restaurants and schools closed, overall demand for dairy showed a 12–15% decline in the U.S. (16), leading to milk surplus and dumping. Whole egg demand increased but liquid egg demand, usually 30% of the U.S. egg market, decreased, leading to plant closures, contract cancellations, and the euthanasia of laying hens. The demand fell for high-end beef usually served in restaurants and farmers and processors struggled to cope with changing levels and types of demand from different sectors. However, the greatest impact of COVID-19 on the livestock product supply chain commenced with disease outbreaks among processing plant workers, leading to plant closures and effects up and down the food chain.

COVID-19 EFFECTS ON HUMAN WELFARE

There are reports of clusters of COVID-19 cases in processing plants in several countries, including Canada, Brazil, U.S., Ireland, U.K., Spain, Australia, Denmark, and Germany (17). In Germany, coronavirus infected more than 1,500 workers in one of Europe's largest meat-processing plants (18). This represents a mass outbreak several weeks after the virus peaked and at a time when the country was "reopening." However, the U.S. remains the hardest hit country where, according to one website, "As of September 11, there have been at least 39,000 reported positive cases tied to meatpacking facilities in at least 417 plants in 40 states, and at least 184 reported worker deaths in at least 50 plants in 27 states." (19). Forty-nine plants were closed for various lengths of time (19), and nearly 200 U.S. Department of Agriculture—Food Safety Inspection Service inspectors tested positive, with four deaths (20). In a study of processing plants in 23 states, 9.1% of workers tested positive during April and May 2020 (21).

Apart from the obvious direct impact on human welfare for those who were infected and became ill or died from the disease, the clusters at processing plants highlighted several inequality issues that contributed to the outbreaks. Firstly, the vast majority of the workforce in meat plants represent migrant and minority workers who are inherently more vulnerable to exploitation (22) compounded by language barriers (23). There is evidence that the disease affects minority workers disproportionately, with Hispanic and Asian workers making up 30 and 6% of the workforce, yet 56 and 12% of the positive cases in U.S. plants (21). Additionally, the processing portion (including slaughter and packing) of farm-to-fork production is inherently more dangerous than non-food system industries (24). Meat, dairy, and fish production is more dangerous than other food production, with relatively high levels of severe equipment-related and assault-related injuries, and more fatalities from assaults from co-workers and animals and exposure to harmful substances (24), together with increased psychological distress among slaughterhouse workers (25). Those on the processing line work in very close proximity where food safety and the risk of zoonotic disease direct hygiene practices, rather than person-to-person disease spread. Superimposed upon these dangers, is evidence of low pay, lack of sick leave and affordable healthcare, together with high density and low quality housing for workers (26).

When processing plants started closing down, the affected workers faced financial uncertainty. Workers elsewhere in the supply chain also faced a period of insecurity when the effects of plant closures became apparent, including job losses, financial impacts, loss of animals, etc. Where plants were still working but with reduced staffing, workloads were increased or duties changed, both likely to increase risk of injury. In some instances, the limits on line speeds were raised by waivers from the USDA-FSIS, again likely increasing worker stress and injury risk, and with potential impacts on animal welfare (stunning effectiveness) and food safety. A record number of 16 poultry processing plants acquired line speed waivers in March and April 2020 (27). This allowed the number of birds being stunned and killed to increase from 140 birds/min to 175 birds/min. Faster line speeds likely contributed to the reduction in the post-mortem condemnation percent which fell 7.7% (a monthly record) to a record low of 0.60% condemned meat by weight (**Figure 1**) in April 2020. After a slight rebound in May, a new record low of 0.58% condemned meat by weight was set in June and July 2020. This indication of possible reduced inspection oversight is supported by the fact that between 2017 and 2020, there is a strong negative correlation between the number of plants with line speed waivers and percent of weight condemned (**Figure 1**). Ultimately, this represents a major threat to public health (and welfare) through reduced food safety (29).

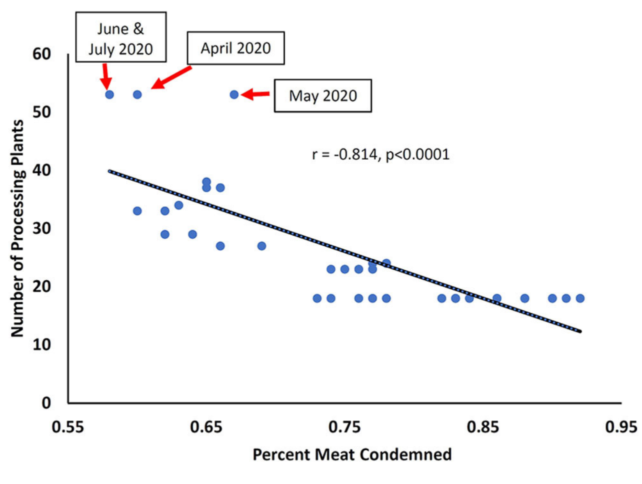

FIGURE 1 | Relationship between number of poultry processing plants given line speed waivers by USDA-FSIS and the percent of chicken meat condemned by weight, between January 2017 and July 2020 [Sources: (27, 28)].

Processing plant closures affected some farmers who, faced with nowhere to send animals for slaughter, had to prepare for and carry out mass depopulation of surplus animals. We detail the impact this had on animal welfare below, but mass depopulation also carries a human welfare cost, for the stockperson and for those tasked with carrying it out. Even at a single animal level, emotional strain on stockpersons is a barrier to the euthanasia of sick animals (30). When moving to a farm population level, the outbreaks of foot-and-mouth disease in the UK showed that affected farmers suffered increased stress, marginalization, and depression (31). The effect was more widespread within rural communities and included "distress, feelings of bereavement, fear of a new disaster, loss of trust in authority and systems of control, and the undermining of the value of local knowledge" (32). Those killing the animals are not immune to the impact, even without the emotional or financial ties of ownership/livelihood. Two years after the foot-and-mouth disease outbreak in Japan in 2010, veterinarians, livestock technicians and even clerical workers interacting with the farmers suffered mental stress (33). To that end, current guidelines include the recommendation that "to mitigate the negative psychological effects of involvement in mass euthanasia activities, psychological counselors should be made available to both staff and the stakeholders" (34).

Finally, a less obvious impact on human welfare is the public health risk posed by carcass disposal (35). Of all carcass disposal methods open air burning and unlined burial of carcasses pose the highest risks of contaminating ground and surface water, soil, and air with pollutants and pathogens like *E. coli* and *Salmonella* (34, 36). Though banned in many countries (36) the U.S. permits both methods for emergency disposal of carcasses (37). Composting is a frequently employed method of disposing of casualty animals on farm and it too poses similar risks if done at scale (37). Additional risks to public health are posed by vectors that feed on carcasses, such as birds, flies, and mosquitos as they can spread biological leachate components (38). On-farm burial and composting, "in-house" in the case of poultry, were among measures employed to dispose of carcasses in the current pandemic. Concerns were raised for public health in areas where carcasses were disposed of using such methods not only because of the risk of pathogen spread but also because of odor and flies (39, 40). Additionally, USDA-APHIS (34) acknowledge the potential for psychological harm caused by the "extremely unpleasant odors and sight of animal remains." Inhabitants of areas where carcasses were disposed of at scale may already be disadvantaged in terms of their health and welfare (41). The air around pig and poultry sites contains hydrogen sulfide and ammonia, particulate matter, and bacteria (42). Such pollutants act as eye and respiratory irritants (43). Unsurprisingly then, inhabitants are more likely to suffer more from asthma and other respiratory diseases (44). Exposure to these pollutants also contributes to mental stress (45) and elevated blood pressure (46). Hence, the threats to public health associated with carcass disposal may compound existing health challenges for people in the surrounding population and may even place them at higher risk of serious complications or death should they contract COVID-19 (40).

COVID-19 EFFECTS ON ANIMAL WELFARE

The biosecurity and pollution risks posed by mass carcass disposal outlined in the preceding section could also adversely affect the welfare of wild animals, fish, birds, and insects which are not discussed in the current paper. Here we focus on the

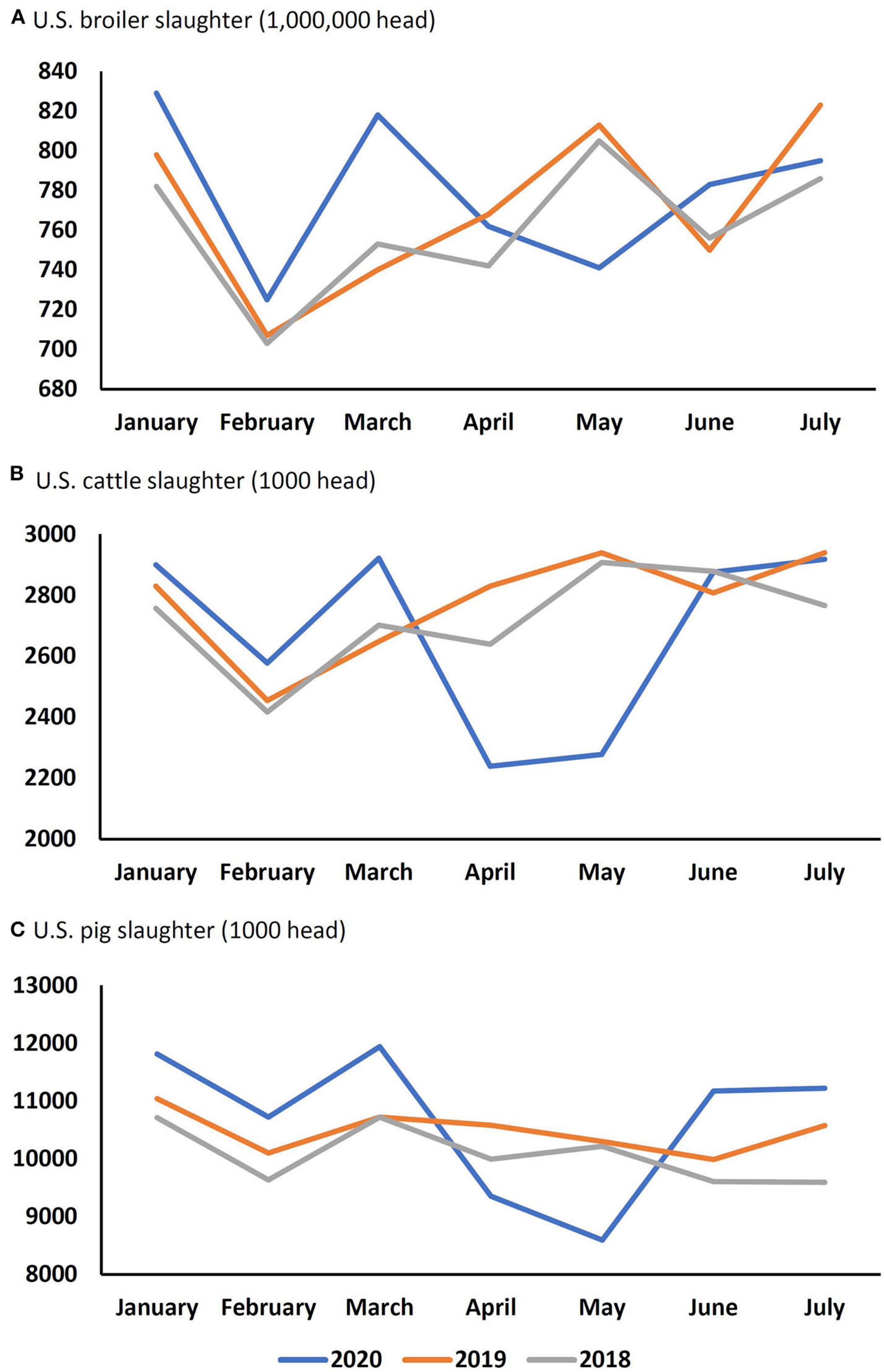

FIGURE 2 | Numbers of **(A)** broiler chickens, **(B)** cattle, and **(C)** pigs slaughtered per month in the United States between January and July over the last 3 years [Sources: (28, 49)].

effects that human clusters of COVID-19 at meat processing plants and the associated decisions to close them, had on animal welfare. Within the U.S., the closures began with a Foster Farms poultry processing plant at Farmerville, Louisiana on March 27th 2020 (19). Over the next 4 weeks, a cascade of closures across cattle, poultry, and pig sectors followed—some closures were only for a few days for deep cleaning, others were longer (47). The result was a loss in slaughter and processing capacity. By the 4th week in April, it was estimated that pig slaughter capacity in the U.S. was operating at only about 55% of normal (48), meaning that about 250,000 pigs a day were at slaughter weight, but had nowhere to go for slaughter. The impact was similar for other livestock industries reflected in the monthly data for all species (**Figure 2**).

By April 28th 2020, the U.S. President invoked the Defense Production Act of 1950, and issued an Executive Order mandating processing plants to reopen. Since then, plants reopened, but many with reduced capacity due to staff shortages. By May 19th, pig slaughter capacity was back to 79.3% of normal, but this still represented a shortfall of over 100,000 pigs per day. For poultry, increasing the number of processing plants operating with line speed waivers recaptured some of the reduced capacity. This allows the number of birds being stunned and killed to increase from 140 birds/min to 175 birds/min. This possibly increased the number of birds exposed to incomplete stunning which poses major concerns for animal welfare (50). With the slaughter end of the chain experiencing reduced capacity, there is an almost immediate impact on animal welfare on farm mostly arising from overcrowding. As detailed above, the poultry and pig industries in particular are intensive and integrated, with little or no flexibility within the production system. When pigs and chickens are unable to leave the farm for the usual slaughterhouse at the designated time, there is an immediate "bottleneck" in the system, because the "production" of new chicks and piglets continues unchecked. With longer gestations and slower growth rates, cattle production is under less immediate pressure. In some cases, there is extra slaughter capacity at other processing plants, but this may increase transportation time and distance, exposing animals and birds to increased transport stress (51).

Intensive pig and poultry production systems are characterized by maximal use of buildings, maximizing the number of chickens or pigs per square area, and the number of days the pens or buildings are in use per year. Each farm has a pre-determined flow with rigid set dates for the animals to enter and leave, based on expected growth rates. Broiler chickens arrive on farm as day-old chicks and are ready to leave at slaughter weight 6–7 weeks later. With a 3-week egg incubation period, the whole production cycle is 9–10 weeks. Pigs in the U.S. move through the farrowing house (3 weeks), the nursery (6–8 weeks) and the grow-finish barn (16–17 weeks) before slaughter. With a nearly 4-month gestation period, the pig production cycle is 41–44 weeks. Without the ability to move livestock off the farm, serious overcrowding occurs within days or a few weeks at most.

For broiler chickens, their phenomenal growth rate causes almost immediate problems in terms of lack of space. For example, if stocked at the maximal EU stocking density of 33 kg/m^2 under minimum welfare standards, this equates to about 13 birds/m^2 at 6 weeks of age (about 2.5 kg/bird). By week 7, there is 42 kg/m^2 and by week 8 there is 48 kg/m^2. EU farms that meet certain extra requirements can stock up to 42 kg/m^2 (52) and meeting this target at 6 weeks of age equates to about 17 birds/m^2. By week 7, there is 54 kg/m^2 and by week 8 there is 62 kg/m^2. Hence, overcrowding from a legal definition occurs within 1–7 days. From a welfare perspective, high stocking densities can lead to decreased walking ability, poorer leg health, increased fearfulness, increased footpad and hock dermatitis and increased mortality (53). Overcrowding-induced increased heat production and associated reduced environmental qualities, such as poorer air and bedding quality exacerbates these welfare issues.

Pigs are selected for increased growth rates but the fact that the birth-to-slaughter time period is 24–28 weeks and is a multi-stage process, means the industry is slightly more flexible compared to broiler production. Modeling exercises determine the impacts that imposed movement restrictions may have with respect to an outbreak of a foreign animal disease (FAD), such as African swine fever (ASF). Increasingly, pig production is on multiple sites, with piglets moving off the breeding farm at weaning or after nursery phase. Modeling for FAD assumes no movement between units whereas the COVID-19 situation allowed it. Without movement between units, breeding-only units can reach critical overcrowding in 4–5 days. Nursery units take 24–52 days, grow-finish units take 78 days and farrow-to-finish units take 43 days (54, 55) to achieve crowding. Effects of crowding for pigs includes decreased general activity and comfort behaviors, increased aggression, skin lesions and tail injuries, increased foot and limb injuries, reduced growth and physiological function, and increased susceptibility to disease (56). The latter increases use of antimicrobials, which in turn increases the risk of antimicrobial resistance.

Clearly, fast growth rates are a major factor in overcrowding. In pigs, methods to decrease growth rates include removal of growth promoters, moving to lower energy diets, reducing feed availability and increasing building temperature to reduce appetite and hence, feed intake (57). Removing growth promotors is likely to improve pig welfare (58). However, anything that reduces feed intake may lead to animals experiencing hunger, a negative affective state (59) and reduced satiety may also lead to increased aggression as animals seek to gain access to a limited resource (60). Likewise, inducing heat stress has detrimental effects on pig welfare (61).

One way to slow or stop new animals and birds entering at the input end is to stop breeding the females. However, as the gestation length is nearly 16 weeks in pigs, it would take that long to feel the impact of this measure. Inducing abortions would have an immediate effect in terms of easing space in the farrowing house, which could be repurposed as nursery pig accommodation. This would relieve pressure up the chain, but only on a temporary basis. For poultry, the chain is much shorter, and a reduction in eggs entering the incubator, results in a reduction in bird numbers within 3 weeks. Alternatively, eggs can be removed from the incubator and euthanized, or chicks killed at hatching. The recommended methods for egg euthanasia are dependent on the stage of incubation. The American Veterinary

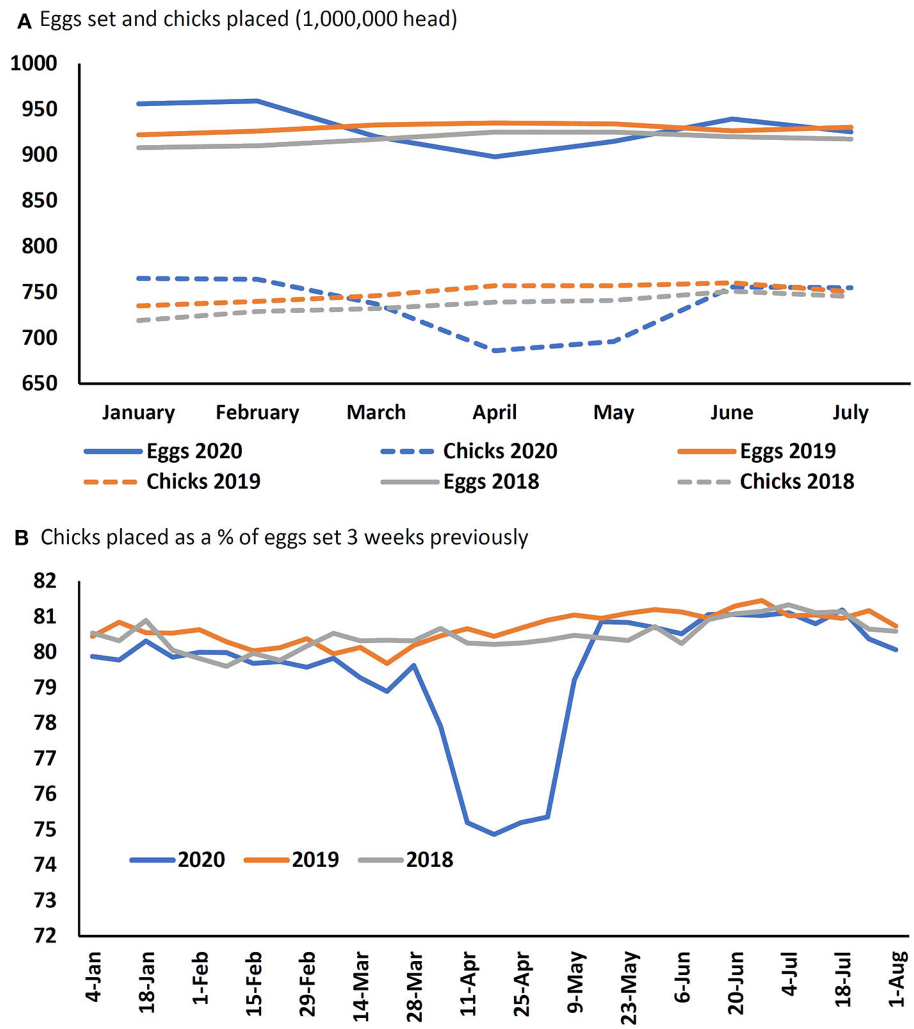

FIGURE 3 | (A) Numbers of eggs set and broiler chicks placed between January and July, and **(B)** broiler chicks placed as a percent of eggs set 3 weeks previously between January and July over the last 3 years in the United States [Source: (68)].

Medical Association (AVMA) Depopulation Guidelines (62) recommend that eggs that are >80% incubated (day 16, chickens; day 22, turkeys, ducks) be treated as per newly hatched chicks, and subject to preferred methods that "include containerized gassing, cooling, freezing, and maceration." Eggs <80% incubated can be euthanized by freezing, cooling to <4°C for 4 h or exposure to high CO_2 concentrations for at least 20 min. Implications for animal welfare of euthanizing eggs are unknown but there are considerable welfare, ethical, and societal concerns surrounding the killing of day old chicks (63, 64). Maceration is often used for chicks up to 72 h old, and under EU regulations, maceration "should result in instantaneous maceration and death of the chicks and embryos (unhatched eggs). The apparatus should contain rapidly rotating, mechanically operating blades." There are a number of identified hazards that may prevent this from happening, such as slow equipment and overloading by handlers (65) and there is likely an increased risk of such hazards when both machines and workers experience higher than normal throughput. Maceration is banned in Switzerland, France, and Germany. Gassing also carries welfare concerns (66, 67), especially with CO_2, with one study concluding that "behavioral signs of distress were observed with all treatments, and occurred at concentrations lower than those causing insensibility" (67). There is some evidence that the U.S. broiler industry carried out egg and/or chick euthanasia, with marked reductions in eggs set and chicks placed, and a lower percentage of set eggs being placed (**Figure 3**).

The worst-case scenario is where the only resolution to the backlog of animals is to kill them on farm. Ideally, this would be by euthanasia, whereby animals have a "good death" without pain or distress. At the very least, emergency killings should observe the same level of animal welfare as during planned killings or standard slaughter. This means as little handling as possible and use of a killing method that either causes immediate death, or sedation followed by death, or death in already stunned/unconscious animals (69). However, this is difficult to achieve when killing animals at scale in an emergency. The most recent widespread need for mass depopulation of animals was in the control of ASF outbreaks and disturbing videos emerged of the burial and burning of live animals in Asia. Within the U.S., the AVMA released updated guidelines in 2019 (62), for use in conjunction with FAD PReP/NAHEMS Guidelines: Mass Depopulation & Euthanasia (34). The Guidelines detail appropriate methods by species, in terms of "Preferred," "Permitted in Constrained Circumstances," and "Not Recommended."

For pigs, the "preferred" methods include gunshot, non-penetrating captive bolt, penetrating captive bolt, electrocution, manual blunt force trauma, carbon dioxide (CO_2) and anesthetic overdose, though the applicability of each method is also dependent on size and age of the pig (62). Permitted in constrained circumstances are ventilation shutdown in combination with additional heat or CO_2 (abbreviated as "VSD Plus"), and dosing with sodium nitrite (62). However, there is little research on some of these methods. For example, sodium nitrite was previously only used in the control of feral pig populations (70) and never for mass depopulation of commercial pigs. Its efficacy is contingent upon pigs being able to ingest a toxic dose in a limited and acceptable, non-defined timeframe (62). As the COVID-19 crisis emerged, the U.S. National Pork Board issued an emergency request for proposals entitled "Animal well-being depopulation field trials" with a deadline of May 11th 2020 to identify projects and started by May 29th 2020. This highlights the paucity of information for pigs. The exact numbers of healthy pigs killed as a consequence of COVID-19 is not yet available, but officials in Iowa, the top pig-producing state in the U.S., estimate that 600,000 animals may need to be euthanized in the state alone (71).

For poultry, different methods are approved depending on whether the birds are indoors or outdoors and if they are floor-reared or caged (62). For floor-reared birds, such as broilers or aviary-housed laying hens, "Preferred methods include water-based foam generators, water-based foam nozzles, whole-house gassing, partial-house gassing, containerized gassing, cervical dislocation, mechanically assisted cervical dislocation, and captive bolt gun. Methods permitted in constrained circumstances include gunshot, VSD plus, controlled demolition, exsanguination, and decapitation" (62). For caged birds, "Preferred methods include whole-house gassing, partial-house gassing, and containerized gassing. Methods permitted in constrained circumstances include compressed air foam, cervical dislocation, mechanically assisted cervical dislocation, captive bolt gun, VSD plus, and decapitation" (62). Whole-house gassing using CO_2 emerged as the major method of choice, together with water-based foam methods. Importantly, The World Organization for Animal Health (OIE) does not condone water-based foam for euthanasia, even in situations of emergency disease control (72). Recently, the European Commission tasked the European Food Standards Agency to examine the scientific evidence surrounding mass euthanasia of farm animal species and identify hazards to animal welfare. The report concerning poultry identified 29 potential hazards, of which 26 were associated with the personnel carrying out the task (65). For both whole-house gassing and foam methods, insufficient time of exposure was a hazard. Timing of the accompanying VSD needs to be appropriate so that the chosen method is the cause of killing, rather than thermal stress caused by VSD itself. As with pigs, the exact number of poultry euthanized due to COVID-19 is currently unknown, but there are reports of the culling of up to 10 million chickens in the U.S. (73).

The potential negative impact of mass depopulation on the welfare of animals and birds is likely enormous. At its most extreme, distressing videos emerged of the need for additional captive bolt killing of pigs still alive after "2–3 h of 140°F heat" following use of VSD Plus (74). Correspondingly, World Animal Protection called on the AVMA to remove this and water based foams from its guidelines of currently approved methods for the depopulation of animals as it causes prolonged heat stress and suffocation (75). In fact there are three major factors influencing animal welfare during the depopulation process (69): (i) handling prior to killing, (ii) the stun/kill quality, and (iii) confirmation of death prior to carcass disposal. Most methods of killing have limitations in one or more of these factors (62). For example, there may be a trade-off between possible distress during a longer time to induce unconsciousness and the benefits of reduced handling of individual animals associated with a particular method. The subjective feelings of the animals subjected to mass depopulation are likely to include, fear, pain, and distress potentially reflected in open-mouth breathing, ataxia, righting responses, escape attempts, and vocalizations (76) among other behavioral signs of suffering.

COVID-19 EFFECTS ON ENVIRONMENTAL WELFARE

Even under normal circumstances, carcass disposal methods pose a pollution risk (35). However, there are major environmental implications associated with disposing of carcasses at scale (38, 77). Furthermore, as pig and poultry industries are often concentrated in specific geographical areas, killing thousands of animals and birds may create a new stream of waste in ecosystems already burdened by environmental pollution [e.g., (78)]. Generally, as carcasses degrade, bodily fluids, chemical and biological leachate components and hazardous gases [e.g., ammonia (NH_3), hydrogen sulfide (H_2S), methane (CH_4), and other air pollutants] are released into the environment, including into the air, surface water, and groundwater. The extent to which there is a risk of this occurring obviously depends on the chosen method (38). However, some of the more risky methods of carcass disposal (38) were employed in the U.S. including unlined burial and composting (40, 79). Both are prohibited in many countries including The European Union (E.U.) under the EU Animal By-Product Regulations 2014.

Composting is a carcass disposal method that promotes decomposition through placement of carcasses between layers (approximately two feet thick) of carbon rich organic materials. With the need for mass carcass disposal, massive quantities of materials like wood chips, corn stalks, sawdust, or straw were needed placing a drain on environmental resources. Under normal circumstances, composting has potential to contaminate the underlying soil and is associated with greenhouse gas (GHG) emissions (35). At scale, increases in ammonia-nitrogen appear to pose the most significant soil pollution hazard (80). Such risks are minimized by use of an impervious base layer, regular turning and covering the compost heaps (37) but this is difficult to achieve in an emergency. Some poultry producers composted chickens in the houses where they were killed by layering the carcasses with straw and "cooking" them under high heat for about a month in what is likely an energy intensive process. However, it can be difficult to successfully compost carcasses in non-purpose built or other "make-shift" type compost facilities resulting in increased GHG emissions (39). Furthermore, dead chicken compost is spread on fields similar to fertilizer and such land application poses "run-off" concerns as it is even higher in phosphorus than manure (81).

At the time of writing, there are no reports of mass depopulation in the E.U. but the need for carcass disposal at scale could change with continuing closures of meat processing plants. If required, it would likely have to be by incineration (either on or off-farm) and rendering both of which are less risky to the environment in terms of contamination (38). However, it is widely acknowledged that neither process could cope with carcass disposal at scale. Assuming limitations with capacity in the few remaining rendering plants operational in the E.U. (35) could be overcome, the process still has a high-energy demand and produces effluent with high biological and chemical oxygen demand. Net GHG emissions can be minimized if some of the by-products (e.g., tallow) are recovered for subsequent energy production. The process also means animals are not wasted completely as rendering claims to recycle meat, bone, and fat into ingredients for numerous products. Incineration of carcasses is also highly energy intensive, exacerbated by the relatively high water content of carcasses meaning that it generates considerable GHG emissions. Large-scale mobile waste incinerator units could be used to process massive volumes of animal carcasses in a biologically safe way. However, there are issues with the operation costs and turnaround time, and ash disposal may cause environmental challenges. There are more environmentally friendly methods of carcass disposal (38). However, processes such as alkaline hydrolysis, are currently too expensive for use in anything but highly specialized operations (82).

As mentioned earlier, killing of poultry in the current crisis often involved foam methods. Water-based compressed air foam (CAF) has its origins in firefighting; CAFs reduce the total water supply to extinguish a fire to as little as one-third compared with applying water alone. However, as a form of mass euthanasia they use copious amounts of water (37). They also contain chemical surfactants and preservatives and certain biological nutrients. Hence, in the case of protein-based foams, breakdown in the environment releases ammonia. Other reported environmental concerns include water pollution/de-oxygenation and the accumulation of the associated compounds in plants and animals (83) although the extent to which these are potential problems associated with its use in mass depopulation of poultry is unknown.

In a somewhat related environmental problem, numerous countries dumped hundreds of thousands of liters of milk because of the fall in demand [e.g., (84)]. Milk dumping poses a serious risk to fish and aquatic life as it reduces oxygen levels if it gets into waterways due to its high biochemical oxygen demand (85). In the U.S., farmers were advised to hold milk in manure storage lagoons if high rainfall was expected as this causes even faster runoff. However, such manure storage lagoons are themselves prone to failure during particularly high rainfall events (86).

Some dairy cooperatives advised farmers to cull extra cows (87). Any form of involuntary culling of animals raises GHG emissions (88). Hence, emergency disposal of farm animals (and their products) represents a dramatic increase in the carbon footprint of food production systems. At its most basic, it also represents an enormous waste of the finite resources (land/feed, water, and fossil fuels) that went into producing those animals and birds in the first place.

WHAT CAN WE DO TO LESSEN THE IMPACT?

The post-World War II industrialization of agriculture was successful in its immediate goal of increasing the amount and affordability of food in developed countries. The costs associated with such a sustained push for more plentiful, cheaper food generally remained hidden when the system was functioning, supported by the general dissociation of food production from food consumption (89). Not surprisingly then, perturbations about our models of food production were mainly related to direct and immediate threats to human health caused by food safety emergencies such as "mad cow disease" or dioxin scares (90, 91). In recent years, the number of publications relating to the additional threats of climate change, biodiversity loss, and antimicrobial resistance associated with food animal production increased (92–94). However, the COVID-19 pandemic revealed the harsh reality about the fragility and high "costs" associated with intensive and highly specialized food production systems like no other threat before (95). The unequivocal detrimental and interrelated implications of COVID-19, for humans, farm animals and the environment outlined in this paper, provides compelling evidence of complex interconnectivities that are captured in the One Welfare concept (12). Indeed, One Welfare reconnects food production with food consumption, the diametric ends of the production chain. Apprehending this connection is crucial if we are to undertake the radical overhaul required of the way in which we currently raise, kill, process, market and consume meat, and dairy products (96, 97). With many environmental systems and processes being pushed beyond safe boundaries by food production the need for change is urgent (97). Indeed, there are threats that a new pandemic is imminent at the time of writing (98). Changes are required at all stages from production through processing and retail to consumption (99, 100). In the ensuing sections, we initially suggest some of the immediate, more short-term solutions that could be implemented at each of these stages.

Production

The need for emergency killing of animals and birds at scale on farm as well as the strategies employed to reduce throughput (slowing growth rates, induced abortions etc.) pose major problems for One Welfare as outlined above. Therefore, in the face of more frequent threats similar to the current COVID-19 crisis, it is imperative that such strategies are avoided completely. Achieving this likely requires the transformative change of current animal production systems referred to above so there are not many immediate, short term solutions. Indeed the tentative suggestions below come at a cost to some aspect of One Welfare and should be limited to exceptional circumstances.

A relaxation of quality assurance/premium product standards, i.e., Global Animal Partnership 5-step Animal Welfare Standards (101), RSPCA Assured (102) etc., without penalty would benefit farmers' emotional welfare as it would prevent depopulation based on failing standards. For example, RSPCA Assured space allowances for 50–85 kg pigs are 0.55–0.675 m^2 per pig. Global Animal Partnership's space allowances for 50 kg+ pigs is 0.93 m^2 on Step 1 or 1.10 m^2 on Step 2. E.U. minimum space allowances for 50–85 kg pigs is 0.55 m^2. If pigs are unable to leave the farm for regular slaughter due to processing plant closures, pressure on space within the system increases. Without relaxation of standards, farmers would have to euthanize animals or risk losing premium payments for failing to maintain scheme standards. Hence, temporary relaxation could not only reduce the number of animals depopulated, but also reduce stresses associated with impending financial distress for the farmer. Clearly such standards assure better quality of production methods with associated benefits to animal welfare and food safety so other aspects of One Welfare would suffer.

The U.S. National Pork Board suggested moving animals into temporary housing or outdoors (103) as a temporary solution to the problem of surplus animals. However, this was an unrealistic option for many producers, for obvious reasons such as lack of an additional, suitable spaces. This "solution" could also constitute an animal welfare risk due to potential exposure of animals to adverse weather, inappropriate climatic conditions (for weaned pigs for example) and difficulty supplying feed or water outdoors. Nevertheless, there is undoubtedly merit in documenting available/empty buildings, land, or other areas that might be suitable to accommodate surplus animals. Producer groups or large integrators could co-ordinate these databases at national or local level and across species. Such a solution would also be useful to help in moving animals to safer locations if there was threat of natural disasters such as flooding. However, it would not be useful in the face of an infectious threat to animal health where movement is prohibited (as in the case of ASF).

Processing

Ideally surplus/additional animals would be slaughtered in the usual way (69) but currently this is not possible given the reduction in processing plant capacity across all species (**Figure 2**), and in many countries worldwide (17). The June 17th estimate for the U.S. pig industry, was a backlog of 3.2 million pigs (104). As with the trend in farm numbers and sizes, there is a similar trend in processing plants, with fewer plants processing larger numbers of animals. In 1970, there were over 7,000 processing plants. In 2020, there are about 2,700, of which the U.S. federal government inspects 835 and which account for about 99% of total slaughter capacity. The range in capacity within these 835 plants is large. For cattle, the U.S. federal government inspects 670 plants but the 12 largest slaughter 52% of the total number. For pigs, the U.S. federal government inspects 619 plants and the 14 largest slaughter 59% of the total number. Hence, if the largest processing plants are closed, the smaller plants have insufficient spare capacity to make up the shortfall, and so until the point at which the processing plants are back online, short-term remedial action could include the following options. Increase capacity at open processing plants. Plants remaining open can achieve short-term increases in capacity by increasing hours of operation, and relocating healthy staff from closed plants. According to the National Pork Board, pig processing plant capacity is based on the plants being open, on average, for 5.4 days per week (48). If individual plants could stay open for 7 days per week, they could increase their capacity by nearly 30%.

There are a myriad of reasons for the worldwide decline in the number of abattoirs, however, burgeoning food safety regulations represent a significant financial burden for these small businesses (105, 106). Such rules are increasingly aligned with global standards and therefore developed for the intensive, large-scale food system, which makes them antagonistic to the practices of small-scale farmers, and local production systems (107). Efforts to address the decline in local abattoirs should include a broadening of the scope of risk analysis (108) to incorporate the benefits to One Welfare associated with local slaughter in small or mobile abattoirs (109, 110).

In the immediate term, it is clear that we need to protect the welfare of humans working in the processing sector better. The meat processing industry is a difficult working environment and regardless of country, there appears to be an increasing reliance on migrant labor to fill positions in what is known as a high employee turnover industry. For example, countries in Western Europe have many migrant workers from Eastern Europe (111). The United States has many migrant workers from Latin America (112). Many plants do not have unionized workforces and many employ undocumented or sub-contracted workers on low wages, with the tacit acknowledgment that the power and major economic benefit lies with the employer. The combination of these social factors and physical factors within the workplace (proximity, ventilation, aerosolization) made processing plants ideal hotspots for clusters to emerge (113). The Centers for Disease Control and Prevention and the Occupational Safety and Health Administration issued joint guidance for processing plants in the U.S. after closing and cleansing (114). Some of these measures include temporary modification of the physical environment; especially increasing spacing between workers, but the longer-term solution requires redesign of processing plants (113). Other guidance focused on the workers, including guidelines to isolate from others during travel to and from work, and staying away from work and seeking medical attention when sick (114). This advice is well meaning, but the current reality is that the combination of low pay, lack of sick leave and medical insurance, crowded social housing and lack of public transport means that much of the advice cannot be followed. There will need to be a longer-term commitment from the processors themselves to invest in their workforce, and improve work conditions, pay, and access to healthcare. The German Agriculture Minister has been vocal in decrying that meat has become a cheap product which does not equate with sustainability, and will introduce legislation to force processing plants to hire employees directly, to end the sub-contract culture and improve worker pay and conditions (115). This will incur cost, and that cost should be met by the combined actors up the supply chain, including retailers and consumers.

Retail

Vertical integration and reliance on large, centralized meat processing plants means there are many opportunities for bottlenecks in the long chain between farm and retail when challenges arise. Distinct differences in the U.S. between supply chains for grocery stores and the food service industry exacerbates this and contributes to the inflexibility of the system. Aligned with a shift amongst certain consumers to the practice of "consumption for the greater good" demand increased for "local" produce or "slow food" in the last few decades (116, 117). This is supplied either through farmers markets (118), or through Community Supported Agriculture. In the latter, families buy "shares" in a farm which supplies them mostly with fruit and vegetables, but also meat, eggs, and dairy, throughout the year (119). Uptake increased greatly during the current pandemic as did interest in these "direct-to-consumer" retail models with some having waiting lists in the hundreds (120). Closure of meat processing plants prompted some farmers to explore alternative methods of sales and distribution. This involved use of online platforms and direct marketing (121), together with farmers markets (122), where still open, and partnering with dine-in restaurants, moving to home delivery. However, such alternative methods are more accessible to those producers who are already part of shorter supply chains, such as those in niche markets or certification schemes such as organic and high welfare (123). Other advantages of this direct approach is economic gain for the farmer and affordability of high quality food for the consumer. For example, organic food in Brazil can be sold direct at farmers markets, without the sometimes 400 times mark-up seen in supermarkets (124).

Consumption

There were several immediate effects of COVID-19 on consumption patterns which if sustained could improve One Welfare. Working from home and the closure of schools and restaurants increased consumption of meals at home, shifting purchasing patterns from restaurants to supermarkets (125). While supermarket freezers were initially emptied of pre-prepared meals there was also increased purchasing of basic ingredients, highlighting an increase in in-home preparation of meals (126) which has potential benefits to human health (127). Sales also soared for meal kit companies, such as Blue Apron and HelloFresh, and also for plant-based meats such as Impossible Foods and Beyond Meat, which saw a 264% increase in sales over March–May 2020 (128). This increase in consumption of plant-based alternatives to meat is controversial. These popular brands are highly processed, and they may be of doubtful benefit to human health, often being served as a meat substitute in an otherwise unchanged "fast food" diet (129). They may have benefits for the environment in that "A Beyond Burger generates 90% less GHG emissions, requires 46% less energy, has >99% less impact on water scarcity and 93% less impact on land use than a ¼ pound of U.S. beef (130)." but these products do contain ingredients from monoculture agriculture and should still be sourced with ethical responsibility. Highly processed plant-based meat alternatives may have a role to reduce overall meat consumption—a 50% reduction of which would have an estimated 35% reduction in GHG gases, a 51% reduction in food's land use (131)—but a diet rich in unprocessed plant-based foods will be more beneficial to One Welfare. A shift away from Western-style, high meat-based diets to others such as the Mediterranean Dietary Pyramid (132), would impact human, animal and environmental welfare, increasing the sustainability of food production and consumption (133).

LONG TERM SYSTEM OVERHAUL

COVID-19 revealed that our current, large-scale, vertically-integrated food systems lack resilience or the capacity to adapt over the short term in the face of disturbance. A proposed food system resilience action cycle (134), would see a system encountering a shock (such as COVID-19 pandemic), absorbing it, reacting to it, restoring output to pre-shock levels, but also learning and building robustness ready for the next disturbance, so that its effect is dampened. We identified some potential learning moments and suggested changes to different components of the food chain to protect One Welfare in the face of future pandemics such as COVID-19. However, the process of building such resilience into the food chain will likely protect One Welfare irrespective of whether the challenge is related to another pandemic or to the "the elephant in the room"—climate change. Climate change represents the biggest threat "with the most unknown consequences for agricultural sustainability" (135), with adverse weather events, drought, flood, and wildfire events becoming more frequent (136) and livestock and crop pests extending their geographical reach (137). Ensuring food system resilience in the face of grand challenges can only come from a global transformation of the current model given that much of the world's population is inadequately nourished and many environmental systems and processes are pushed beyond safe boundaries by food production (97). We are perhaps fortunate that the COVID-19 pandemic has elucidated what lies ahead and, if acted upon, will enable us to hit reset and change while we still can.

Globally, we need to move away from the concept that Western industrialized agriculture, and aquaculture, and especially its intensive livestock and fish production systems, are the panaceas that will end food insecurity, even with a growing population and the increasing demand for animal protein. For global animal agriculture, at any one time, there are about 25 billion poultry, 2.25 billion sheep and goats, 1.5 billion cattle and 1 billion pigs (138). Every year, we consume 50 billion chickens, 1.5 billion pigs, 1 billion sheep and goats and 300 million cattle and about 173 million tons of fish, with about 80 million tons farmed (139). These numbers are currently increasing year-on-year as the industrialized model of livestock and fish production spreads to developing countries, especially in Asia (140) with associated increases in antimicrobial use (141) and other costs to One Welfare. The damage associated with the overriding focus on production efficiency could be addressed by a more holistic interpretation of efficiency such as that offered by the One Welfare approach which safeguards animal, human, and environmental welfare.

The European Union Farm to Fork (F2F) Strategy (142) appears to have a One Welfare approach at its core with its aim to transform food production into a "fair, healthy and environmentally-friendly food system." F2F proposes changes to the whole supply chain, focusing on sustainability at all stages—shortening the chain and moving away from the "industry to fork" system (143), and adopting methods to reduce the environmental impact of production, manufacture, processing, retailing, packaging, and transportation, while preserving affordability, ensuring fair distribution of economic returns and safeguarding agri-food workers' safety and welfare. The strategy also states that animal welfare must be improved and that there must be less reliance on pesticides and antimicrobials, and biodiversity loss reduced and reversed. F2F acknowledges the interconnectedness of the planet and the global nature of trade, and hence that "change" needs a global approach. As the EU is the world's major exporter and importer of food it is well-positioned to influence global transformative change by adapting trade policies aligned to the One Welfare approach.

Likewise, the United Nations Sustainable Development Goals (SDGs) will help guide transformation of our food systems (144). One Welfare is implicitly embraced in the 17 goals to "end hunger, achieve food security and improved nutrition and promote sustainable agriculture." For example sub-Goal 2.4 states that "By 2030, ensure sustainable food production systems and implement resilient agricultural practices that increase productivity and production, that help maintain ecosystems, that strengthen capacity for adaptation to climate change, extreme weather, drought, flooding, and other disasters and that progressively improve land and soil quality" (144). At first glance, animal welfare only applies to Goal 2 though even here it is not explicitly mentioned. However, a deeper examination of the SDG agenda revealed that out of 169 targets, 66 are relevant to animal welfare (145). More importantly, relationships between the SDGs and animal welfare were all positive, such that there was no situation where attainment of the SDG conflicted with improving or safeguarding animal welfare (145).

In spite of the tacit One Welfare approach in the F2F strategy and the SDGs, the lack of a specific focus on animal welfare is concerning. As animal welfare scientists, we are convinced of the importance of animal welfare in the development and delivery of solutions to global challenges while urging engagement as part of the interdisciplinary teams working on them (7, 146). In fact, framing animal welfare as the primary driver within the One Welfare concept is likely well-founded for a number of reasons. Firstly, there is a strong relationship between caring for animals, for a species, and for an ecosystem and this relationship is key to encouraging humans to conserve resources and protect the environment [e.g., (147)]. Farm animal welfare also plays a major role in driving animal health, performance and food safety all of which are crucial to the sustainability of animal production systems (148–150). In fact, improvements to animal health leads to a similar reduction in the carbon footprint of livestock farming as breeding for higher productivity but without the associated costs to welfare (151). We urge the strong support of such "win–win" strategies as they address both environmental and ethical sustainability. We stress that the consequences of current and future strategies for animal welfare must be scrutinized and contrasted against their effectiveness in mitigating climate change to identify the most cost-effective measures for improving environmental sustainability of livestock production. Similarly, others conclude that the welfare of farmed and wild animals should be central to the development of sustainable agriculture (152). This is even though concerns have been voiced (and allayed) that increased agricultural efficiency will inevitably conflict with animal welfare (148).

Hence, intensification *per se* is not necessarily bad, but it is imperative to practice sustainable intensification (153). Indeed, notwithstanding the problems posed by the focus on production efficiency, there is a need to increase agricultural output globally to deliver sustainable food security. However, there must be simultaneous progress on inputs such as moderating demand for livestock products (100) and decreasing food wastage, estimated at between 11 and 60% depending on the commodity (154). There should be focus on increasing yield per unit of current cultivated land mass, rather than increasing quantity of cultivated land mass. It may be that yield increases cannot be achieved everywhere and that some land is appropriate for management systems that promote biodiversity whereas other land may not be, and that it is better to intensify and "sacrifice" some land to monoculture agriculture, leaving other land to maintain full biodiversity rather than impact the biodiversity of all land to some extent. Others would argue that such a "land sparing" approach assumes that the functionality of biodiversity in agroecosystems is negligible (155). They suggest that a "land sharing" approach acknowledges the crucial ecosystem services provided by wildlife friendly farming and agroecological intensification. Silvopastoral systems, pastures with shrubs and trees as well as herbage, are an example of a land sharing approach which can be more productive than pasture alone and which confers high levels of welfare to farmed and wild animals whilst at the same time improving human and environmental welfare (152). At the other end of the spectrum the "high tech" Kipster farm produces One Welfare friendly (carbon neutral) eggs in a system that employs "low-opportunity-cost feedstuffs" (156). Clearly, there is not a "one size fits all" solution (153, 157). We must create context specific solutions, which are best developed by rigorous collaboration between disciplines (158), which consider individuals, communities, populations, and ecosystems (159) and which are supported by connected research, incentives, and political will (135).

COVID-19 raised a myriad of One Welfare concerns associated with livestock production. In so doing it has highlighted the fractures in our current food system like no other challenge before. Our fragile food system requires urgent and radical change to build resilience and ensure food security in the face of future challenges, including climate change. Fortunately, COVID-19 also presents us with a unique opportunity for a One Welfare driven transformation of the food production system. This will ensure a resilient, safer, fairer, and potentially healthier environment for both humans and animals in the future.

AUTHOR CONTRIBUTIONS

JM-F and LB participated equally in the conception, writing, and refining of the article.

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Corrigendum: COVID-19 Effects on Livestock Production: A One Welfare Issue

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In the original article, there was an error. **An incomplete disclaimer was used.**
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The authors apologize for this error and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Emerging Zoonotic Diseases: Should We Rethink the Animal–Human Interface?

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INTRODUCTION

Humans have always been plagued by epidemics caused primarily by infectious diseases that originated from animals, especially wildlife (1). The establishment of sustained transmission from initial spillover events involves the interplay of complex mechanisms that are difficult to understand. However, there is consensus that direct or indirect contact of humans with animals and their body fluids (an "animal-human interface") is essential for a successful cross-species transmission. Whilst humans have coexisted with domestic and wild animals for millennia, several anthropogenic factors have intensified the animal-human interface in recent decades, increasing our interactions with animals, and consequently, the risk of disease spillover. This increased intensity is largely driven by human population growth and efforts to alleviate the associated poverty, which include intensified farming and unsustainable exploitation of natural resources. Culinary traditions that include wildlife-meat consumption or traditional medicine also drive trade of wild animals, which can contribute to infectious disease emergence (2). In an increasingly globalized planet, a spillover event that results in an efficient and sustainable transmission between humans can spread very quickly. This has been well-demonstrated by the ongoing coronavirus disease (COVID-19) pandemic that resulted in an unprecedented global public health, social, and economic crisis. The current pandemic also illustrates that, despite our experiences with emerging zoonotic diseases (EZDs) such as Severe Acute Respiratory Syndrome (SARS), Ebola, and highly pathogenic H5N1 avian influenza, and subsequently improved national and global surveillance systems, humanity is not able to prevent new EZDs originating from animals. It is therefore crucial to re-evaluate potential sources of emerging pathogens at the animal-human interface and to examine whether we can minimize the risk for future pandemics at this point. We discuss important interfaces that drive zoonotic disease emergence and spread, and then discuss the feasibility of reducing the risks of EZDs at these interfaces.

WET MARKETS AND OTHER LIVE ANIMAL MARKETS

The definition of a "wet market" can vary with context. Here, we refer to fresh-food markets in which live animals are sold, most commonly for food or medicine, and are slaughtered at the market. This type of market is common throughout Asia, where live animals such as fish, crustaceans, poultry (live bird market sections), various mammals, and other fresh products such as vegetables, are sold. Despite the rapid expansion of supermarkets in Asia, studies have shown that up to 77% of consumers choose wet markets as their primary source of fresh food because they prefer fresh meat (3, 4).

Wet markets have been stigmatized in recent years due to their association with potential infectious disease emergence, such as avian influenza transmission in live bird markets (5, 6). Some wet markets also sell wild animals (wildlife markets), such as reptiles, porcupines, and other species. The SARS virus outbreak (2002–2003) that killed 774 people likely originated from masked palm civets (*Paguma larvata*) sold in wildlife markets in Guangdong Province, China (7). The ongoing COVID-19 pandemic is thought to have originated at the Huanan seafood wholesale market in Wuhan (China). This seafood market also sold live wild animals, such as several species of birds, reptiles, and small mammals, suggesting a possible zoonotic transmission from wildlife to humans (8). Eating wild animals is a symbol of wealth, and their meat is perceived to be more natural and nutritious than meat from farmed animals, and is also an ingredient in traditional medicines (9). Wet markets are often characterized by poor hygiene (10, 11) and the presence of live animals kept in crowded conditions. Together with the difficulty of hygienically selling food in such environments, another risk factor for EZDs is the largely undescribed virus diversity that can been found in some wildlife orders, such as bats, rodents and primates (12). Wild animals that have been removed from their natural habitat, and are housed in conditions that do not promote their welfare, will suffer from severe stress, potentially causing immunosuppression and shedding of pathogens that they may be carrying (13, 14). Despite the warning of the SARS outbreak, COVID-19 emergence has demonstrated that the consumption of freshly slaughtered meat and wildlife is an entrenched activity, and therefore, the sale of live animals, including wildlife, in markets is resistant to change.

WILDLIFE HUNTING AND CONSUMPTION

Hunting and gathering only started to be replaced by livestock breeding and agriculture about 10,000 years ago (15). In some regions of the world—mainly in the tropics where livestock is poorly developed—wildlife hunting and consumption is still commonly practiced, with such meat known as "bushmeat," particularly in Africa (16). In these contexts, wildlife represent a major source of protein and/or income through the sale of meat, large-game tourism (17–19) and trading products for traditional medicine (20), and are also valued for traditional hunting and ceremonial events (21–23). In this context, any activity manipulating wildlife species provides an animal-human interface facilitating a potential pathogen spillover (24). Hunters (mainly men), as well as any person handling dead animals during trade and cooking (mainly women), are exposed to potential pathogens present in animal carcasses and their body fluids. The human immune-deficiency virus (HIV) originated from non-human primates and it is suggested that contacts with hunted primates were responsible for the spillover of this virus to humans (25, 26). Bushmeat consumption has also been implicated in the emergence of Ebola virus disease, resulting in several outbreaks in Central Africa over the last five decades, as well as the large epidemic in West Africa in 2013–2016 in which over 11,300 people died (27, 28). Fruit bats were identified as a reservoir species and spillover to humans happened directly or indirectly *via* an intermediate wildlife species (29, 30). For example, in the West African outbreak, a single spillover event from a fruit bat to a human was suspected to have resulted in sustained human transmission without further animal involvement (28). In contrast, in some of the Ebola virus outbreaks in Central Africa, chimpanzee, or gorilla carcasses were identified as sources of human infection (27), highlighting the important role of species that are closely related to humans for zoonotic spillover.

INTENSIVE WILDLIFE FARMING

Several species of mammals—for example, deer (31), rodents (32), civets (33), and fur mammals—are bred under a wide range of production systems worldwide, and provide income and protein. The legal and technical framework for these production systems is often poor (33, 34) and published information on the biology, production and health of these non-conventional captive species is scarce, particularly in low-income countries (35). Consequently, health-monitoring programs in wildlife farms are seldom implemented, despite intensive farming conditions and low genetic diversity (34, 36). These factors expose farmed wildlife species to stress and immunosuppression (13), and predispose captive wild animal populations to disease emergence. This is illustrated by the circulation of avian influenza strains in ostrich (*Struthio camelus*) farms in South Africa (37), the occurrence of repeated rabies outbreaks in ranched kudu *(Tragelaphus strepsiceros)* populations in Namibia (38), and the recent detection of SARS-CoV-2 circulation in mink (*Neovison vison*) farms in the Netherlands (39).

DOMESTIC ANIMALS—LIVESTOCK AND PETS

Although there are relatively few domesticated species, livestock and companion animals have interfaces with both wildlife and people, and therefore have an important role in the complex pathways leading to EZDs.

Intensive livestock farming is increasing worldwide, encouraged by market demands including urbanization and expanding global populations which have changed the way in which food is produced and supplied (40). Concurrent anthropogenic factors, such as changes in land-use, provide new wildlife-domestic species interfaces by creating shared ecologies, with opportunity for spillover and amplification of new EZDs (41). Nipah virus emergence in Malaysia in 1998 is one such example (42). Dual–agriculture of intensive pig farming with mango plantations created a bat-pig interface that allowed spillover of Nipah virus from bats feeding on the fruit trees to pigs housed below. Repeated spillover events from bats resulted in prolonged circulation of the virus in pigs, increasing

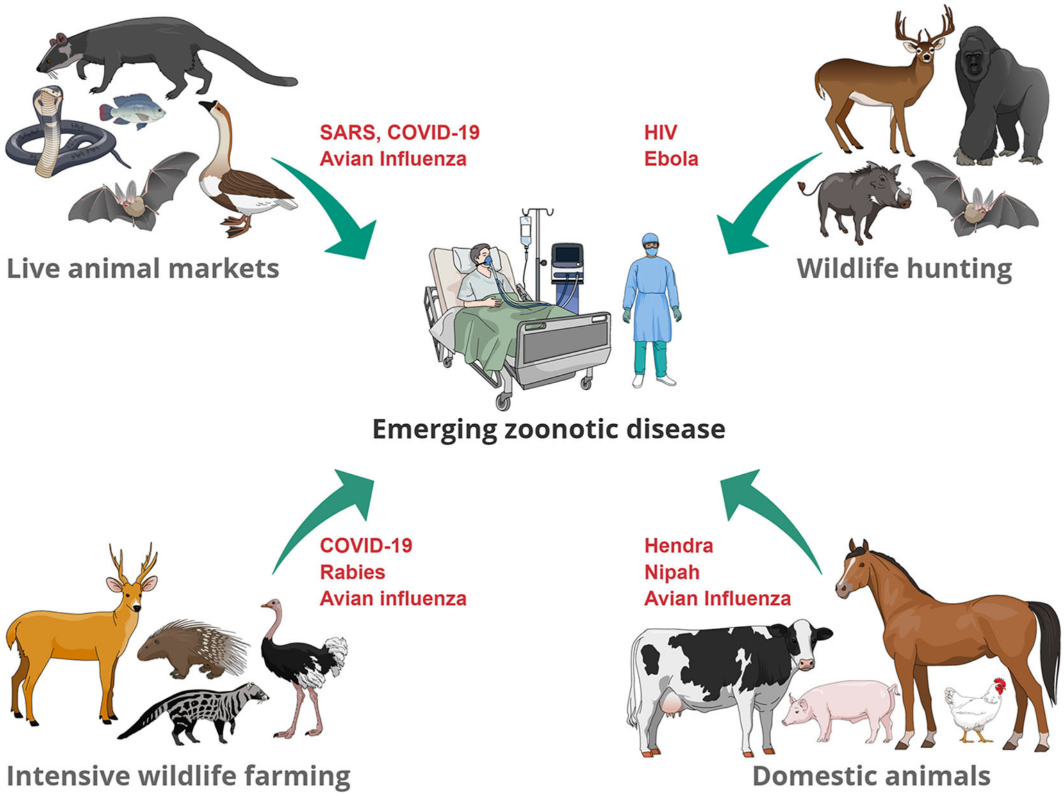

FIGURE 1 | Examples of zoonotic diseases that have (re-) emerged at the animal-human interface. Transmission pathways include direct contact through handling of living animals (wildlife trade, domestic animals), preparation of slaughtered animals for consumption of meat or for traditional medicine uses.

the opportunity for spillover to people (43). This illustrates that large, dynamic populations of a single livestock species can increase the risk of EZDs in people by enabling persistence of a potential pathogen at the livestock-human interface. Mixing of domestic species can also give rise to EZDs; for example, avian influenza viruses circulate and re-combine in domestic poultry in live-bird markets (44). Examples in which companion animal species have provided an interface for EZDs between wildlife and people include Hendra virus (45) and *Chlamydia psittaci* (46). These examples illustrate multiple epidemiologic scenarios involving individual, mixed, or large dynamic domestic animal populations that provide an intermediate interface between wildlife and humans.

DISCUSSION

Our presentation of the different interfaces and potential sources of EZD (**Figure 1**), demonstrates a recurring theme of intensified anthropogenic factors driven by cultural and socioeconomic interests. The challenges for many of these interfaces include achieving a balance between sustainably managing resources required for human population growth, safeguarding species conservation and biodiversity, securing animal and human health, and respecting animal welfare, when large numbers of species are kept in confined spaces (for example, farms and markets). Such use of animals also gives rise to ethical questions related to animal husbandry. Animals' fundamental interests should not be sacrificed if it were not for weightier human interests. This means that the use of animals is, in some contexts, morally permissible (for example, when there is no healthy plant-based alternative to meat), while in other contexts, it is morally problematic (for example, when wild animals are traded and consumed as a symbol of wealth). Whilst it is unrealistic to expect immediate changes in the way humans exploit animals without addressing underlying drivers of this behavior, more consideration should be given to the living conditions of animals in intensive livestock/wildlife farms and in live-animal markets. Less crowded living conditions and respect for biological and behavioral needs of species (such as foraging and occupational opportunities) will not only improve the animals' wellbeing, but also result in lower stress and therefore lower risk of spillover.

Popular reactions to EZD emergence often target the immediate source, rather than underlying drivers. For example, some have suggested shutting down wildlife markets (47). However, as the drivers of wild-animal meat consumption will persist even after a global health crisis, this is likely to shift the interface elsewhere, out of sight of the regulators (48–50). In our opinion, such bans could lead to the emergence of further illegal, unregulated wildlife markets and increased poaching, which would make it impossible to monitor market dynamics, develop surveillance systems, and implement risk mitigation measures. In addition, the interconnectedness of the different interfaces discussed here is illustrated when wildlife hunting is replaced by livestock farming. Some farming practices result in deforestation of large areas (51), and this in turn provides a livestock-wildlife interface and therefore, the potential risk for pathogen spillover from wildlife to livestock. The interconnectedness and complexity of these ecologies demonstrates the need for that holistic approaches according to the One Health and Planetary Health concepts. Both concepts follow the principle that human, animal, and environmental health cannot be separated, and therefore, to solve health problems, all three health fields and the sustainable use of natural resources have to be considered (52).

The focus has been on early detection and rapid response to EZDs in our efforts to control their impacts. Epidemiologists have many tools that can be integrated—for example, horizon scanning, prioritization, and disease modeling—to provide a greater awareness of the EZDs, as well as provide insights for their control (53). Whilst many improvements using integrated tools can still be made across systems for disease preparedness (54), we now also call for actions to reduce the rate of EZDs at the human–animal interfaces. Such actions could include improving hygiene, animal welfare, disease surveillance and safeguarding species conservation through comprehensive and culturally tailored regulations. This will require, in many circumstances, a greater understanding of the sociocultural drivers. For example, the application of social and ethnographic sciences could provide insights about the sociocultural context of wildlife exploitation and trade, and identify potential solutions to promote healthier bushmeat consumption and trade, particularly in tropical forest regions in which livestock farming is poorly developed (35).

In addition, wildlife production systems should be supervised and monitored by international bodies in a comparable way as international certification agencies already control forestry exploitation activities to ensure sustainable wood exploitation (32). Similarly, we need regulation of wildlife farms in the same way that mainstream agriculture is regulated to control welfare and biosecurity conditions. Although wildlife farms represent a minor contribution to national economies, they can have important implications in terms of public health (and we have now seen how that affects economies). Also, alternative protein sources such as aquaculture should be explored; the large diversity of farmed species in aquaculture provides a wide range of opportunities for many countries, while the risk of zoonotic disease emergence is negligible when compared with terrestrial species.

Due to the anthropogenic nature of drivers of EZDs (increased human population, globalization, climate change) changes require government-level strategies that are integrated globally, as well as raising awareness through targeted education of stakeholders including consumers and farmers to improve pathogen surveillance, animal welfare, and reduce environmental impacts of livestock and wildlife farming. With massive human population growth, globalization of trade and travel, and unsustainable use of natural resources, humanity is in a critical phase in which we head toward irreversible global crises. The more we focus on our short-term anthropocentric model of development, the more our coexistence becomes disconnected from nature. This has been proven to have serious and devastating consequences for humankind, such as the impact of EZDs, and for the planet (52). As demonstrated here, the challenges associated with risk mitigation and control of EZDs are tightly interlinked with global sustainability. We therefore appeal for more sustainable animal harvesting and production practices, with a stronger focus on health, and not solely productivity. This will not only reduced the risk for EZDs, but also improve environmental balance and animal welfare.

AUTHOR CONTRIBUTIONS

IM and SD conceptualized the manuscript. IM wrote the introduction, the part about wet markets and other live animal markets and designed the figure. VB wrote the part about domestic animals-livestock and pets. FJ wrote the part about intensive wildlife farming. AM provided input on animal ethics. DP provided input on all topics and the discussion. SD wrote the part about wildlife hunting and consumption and the main body of the discussion. All the authors contributed in the discussion and editing of the manuscript. All the authors have read and approved the manuscript.

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Coronavirus Infection of the Central Nervous System: Animal Models in the Time of COVID-19

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Naturally occurring coronaviral infections have been studied for several decades in the context of companion and production animals, and central nervous system involvement is a common finding, particularly in cats with feline infectious peritonitis (FIP). These companion and production animal coronaviruses have many similarities to recent human pandemic-associated coronaviruses such as SARS-CoV, MERS-CoV, and SARS-CoV2 (COVID-19). Neurological involvement is being increasingly recognized as an important clinical presentation in human COVID-19 patients, often associated with para-infectious processes, and potentially with direct infection within the CNS. Recent breakthroughs in the treatment of coronaviral infections in cats, including neurological FIP, have utilized antiviral drugs similar to those currently in human COVID-19 clinical trials. Differences in specific coronavirus and host factors are reflected in major variations in incidence and mechanisms of CNS coronaviral infection and pathology between species; however, broad lessons relating to treatment of coronavirus infection present within the CNS may be informative across species.

Keywords: GS-441524, remdesivir, SARS-CoV-2, feline infectious peritonitis (FIP), treatment

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INTRODUCTION

The Coronaviridae family of viruses are single-stranded RNA viruses found in a variety of species including cats, dogs, horses, mice, birds, pigs, bats, camels, whales, and humans (1). Coronaviruses are grouped into four genera; alpha, beta, gamma, and delta (**Table 1**) and viral particles contain four main structural proteins, namely, spike (S), envelope (E), membrane (M), and nucleocapsid (N) with specific coronaviruses also having a unique set of accessory proteins (2, 3). The distinctive trimeric spike protein (S) is primarily responsible for recognition of cellular receptors associated with viral binding and potentially internalization of host target cells (2–4). Many key receptors interacting with the spike proteins have been defined for the known coronaviruses (**Table 1**).

Coronavirus infections typically affect the respiratory or gastrointestinal tracts; however, coronavirus-related neurological disease is receiving increased attention as the COVID-19 (SARS-CoV-2) pandemic progresses. Neurological manifestations of COVID-19 infections in humans have become more widely recognized as a significant component of clinical disease (5–16); however, coronavirus involvement of the nervous system is not unique to the SARS-CoV-2.

Several coronaviruses have been associated with neurological disease as a common clinical presentation (**Table 1**), including feline infectious peritonitis (FIP), porcine hemagglutinating encephalitis virus, murine hepatitis virus (MHV), and currently with SARS-CoV2 virus in COVID-19 patients. Less commonly, the human respiratory disease coronaviruses HCoV-299E and

TABLE 1 | Coronaviruses of humans and domestic animals.

Genera	Species	Virus	Disease association	Receptor
Alpha Coronavirus	**Cat**	**FCoV Ser I**	Feline infectious peritonitis	Unknown
		FCoV Ser II	Feline infectious peritonitis	APN
	Human	HCoV-NL63	Respiratory disease, gastroenteritis	ACE2
		HCoV-229E	Respiratory disease	APN
	Pig	TGEV	Transmissible gastroenteritis	APN
		PEDV	Endemic diarrhea	APN
		CSeCoV, SADS-CoV	Diarrhea	Unknown
		PRCV	Respiratory disease	APN
	Dog	CECoV	Enteric disease	APN
Beta Coronavirus	**Human**	**SARS-CoV-2**	COVID-19	ACE2
		SARS-CoV	Severe acute respiratory syndrome	ACE2
		MERS-CoV	Middle East respiratory syndrome	DPP4
		HCoV-HKU1	Respiratory disease	Sialic acids
		HCoV-OC43	Respiratory disease	Sialic acids
	Pig	**Porcine hemagglutinating encephalitis virus (PHEV)**	Vomiting-wasting/encephalomyelitis	NCAM
	Mouse	**Murine hepatitis virus (MHV)**	Hepatitis/encephalitis	CEACAM1
	Cow	BCoV	Enzootic pneumonia/Diarrhea-enteritis	Sialic acids
	Dog	CRCoV	Respiratory disease	Sialic acids
Gamma Coronavirus	**Avian**	IBV	Infectious bronchitis	α-2, 3-Linked sialic acid
Delta Coronavirus	**Pig**	PDCoV/PCoV-HKU15	Diarrhea	APN

APN, aminopeptidase N; ACE2, angiotensin-converting enzyme 2; DPP4, dipeptidyl peptidase-4; NCAM, neural cell adhesion molecule; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1. Viruses in red represent coronavirus disease commonly presenting with neurological signs.

OC43 have been demonstrated in brains of multiple sclerosis (17–21) and encephalitis patients (22–24). Coronavirus-associated encephalitis has been reported in children (25), and sporadic neurological disease has been reported in human Middle Eastern Respiratory syndrome (MERS) and SARS-CoV patients (26–33) although in a relatively limited manner compared to SARS-CoV-2 patients (27, 28, 34).

MECHANISM OF CNS ENTRY

Several mechanisms of entry of coronaviruses into the CNS have been postulated and vary depending on the specific coronavirus, host factors, viral dose, and site of infection. Mechanisms are incompletely or poorly understood in many species; however, hematogenous spread via capillary endothelial cells, retrograde axonal transport via olfactory, pulmonary vagal and enteric neurons, exosomes, and entry via macrophage/monocytic cells have been suggested as potential mechanisms (35–41). Porcine hemagglutinating encephalitis virus has been shown to infect the CNS via retrograde transport in peripheral nerves from primary sites of replication (40, 42), and a similar mechanism of entry has been shown for neurotropic strains of MHV (43) and in a SARS mouse disease model (37).

S protein interaction with cell surface receptors (**Table 1**) is a major determinant of virus virulence and tropism allowing cell binding; subsequent cleavage of the bound spike protein by cellular proteases such as transmembrane serine protease 2 (TMPRSS2) allows internalization by direct fusion with the plasma membrane or use of endocytic mechanisms. Specific coronavirus target receptors have been shown to be variably expressed in a variety of infected CNS cell types (36, 44, 45); however, virus–host interactions are complex as not all infected cells necessarily express a single receptor, additional mechanisms such as receptor independent fusion can occur (46), and binding and entry may utilize similar or different receptors for some viruses (47). Major receptors for the CNS-tropic coronaviruses have been defined in most species, including angiotensin-converting enzyme 2 (ACE2) utilized by human coronaviruses HCoV-NL63, SARS-CoV, and SARS-CoV-2; however, the specific mechanism by which the pre-dominant Type I pathogenic feline coronaviruses attach and enter host cells is poorly defined (48–50).

MECHANISM OF CNS DISEASE

Viral-mediated CNS damage may arise due to direct effects of viral replication within target cells and as a consequence of the vigorous inflammatory response that may have both positive anti-viral and potentially negative secondary effects (51, 52). Profound activation of inflammatory and immune cascades driven by a variety of cytokines and chemokines, including IL6, CXCL10, IL1, IFNγ, and TNFα have been documented in CNS coronavirus infections in a variety of species (11, 25, 37, 51, 53–55). Secondary immune-mediated mechanisms of pathology have also been described relating to the presence of viral antigens and antibody-mediated type III hypersensitivity vasculitis (56, 57). Although poorly defined, coronavirus CNS infections may also result in more chronic disease, as is seen with some strains of MHV (51, 56), and human coronavirus infection has been implicated in the pathogenesis of chronic conditions including Parkinson's disease, multiple sclerosis, and peripheral neuropathies (7, 12, 17, 19, 58).

Clinical and pathological findings in the most commonly affected species with CNS-associated coronavirus diseases is quite variable and likely reflects the variability in cellular tropism, mechanism of infection, and-immune mediated characteristics of disease in the different species. Para-infectious mechanisms, with neurological consequences secondary to extra-CNS disease factors such as sepsis and vascular disease, may also be important when the CNS is not the primary target organ as is the case for COVID-19 patients with acute respiratory disease (5, 7, 8, 59, 60).

Feline Infectious Peritonitis

Feline infectious peritonitis virus is a pathotype of the feline enteric coronavirus (FECV) arising through specific mutations in key viral genes [reviewed in (38)]. Feline infectious peritonitis is named for the more commonly presenting effusive "wet" form of the disease, with a less common "dry" form characterized by granulomatous disease in the absence of marked inflammatory exudation into body cavities (57). Both FECV and FIP biotypes exit as one of two serotypes (61, 62). Type I is the more common serotype and possibly more likely to cause disease (62–64), while type II represents a recombinant between feline and canine enteric coronaviruses (65). Neurological involvement with FIP is well-documented (57, 66–70), occurs in ∼30–40% of cats presenting with the non-effusive form of the disease (57), and is almost universally fatal (57).

Coronavirus infections resulting in FIP do not generally infect primary CNS cells. Pathogenic transformation of the FECV to the FIP biotype involves a marked alteration of tropism from apical epithelial enteric cells to internalization and replication within macrophages/monocytes (71, 72) that pre-dominantly represents the infected cell population within the CNS. Histopathology reflects the pre-dominant immune-mediated perivasculitis mechanism of disease with a lymphoplasmacytic infiltrate and variable presence of macrophages and neutrophils, often perivascular and typically centered around the leptomeninges and ependyma. Lesions particularly affect the caudal brainstem with perivascular oriented meningitis, periventricular and superficial encephalitis, and choroiditis with secondary hydrocephalus (57, 66, 67, 70).

Mouse Hepatitis Virus

Unlike FIP virus, MHV is capable of infecting ependymal cells, astrocytes, microglia, oligodendrocytes, and neurons (56, 73). Depending on specific virus and mouse strain as well as route of infection, a variety of neuropathologies are seen with MHV infection, from acute encephalitis to a more chronic encephalomyelitis and demyelinating disease (56). Mixed inflammation with a significant neutrophilic component is typically present often centered around the choroid plexus, ependyma, and meninges (51, 74, 75).

Porcine Hemagglutinating Encephalomyelitis Virus

In contrast to MHV, PEHV causes a non-suppurative encephalomyelitis with lymphoplasmacytic cuffing involving the gray matter of the cerebrum and neuronal degeneration of the brainstem and trigeminal ganglia (42). Viral infection is restricted to the neuronal perikaryon following spread from primary sites of replication via the peripheral nervous system (40, 76).

Human CNS Coronavirus Infection

Detailed reports of cell tropism and histopathological lesions in human patients with coronavirus-associated neurological disease are lacking. SARS-CoV and HCoV-OC43 have been reported in cerebral neurons from autopsy specimens using immunohistochemistry and *in situ* hybridization (23, 32, 33, 77), and coronavirus has been similarly reported in unspecified cells from MS patients (17, 20). Neuronal degeneration, gliosis, and cerebral edema were the most consistent findings reported in SARS patients where histopathology of the brain was described (32, 33) and involvement of brainstem neurons has been proposed as a component of respiratory failure seen in patients (78, 79). Findings in COVID-19 patients are limited and variable. The most common underlying mechanisms of CNS involvement in COVID-19 patients remain to be defined (10, 80, 81), and direct evidence of virus in the CNS is limited. However, SARS-CoV-2 virus has been demonstrated specifically in the CSF (6, 80, 82, 83) and in brain tissue in up to 36% of COVID-19 patients examined at autopsy (59, 60, 84, 85). Variable neuropathological findings have been reported including subcortical white matter vascular and demyelinating lesions (86), lymphocytic meningoencephalitis with prominent neuronal loss (79), and hypoxic injury (60). Neuroimaging with MRI in 37 patients was similarly variable with common findings including signal abnormalities in the medial temporal lobe, multifocal white matter hyperintensities, and extensive white matter microhemorrhages (80).

Clinical neurological signs associated with the COVID-19 SARS-CoV-2 virus are variable and have been commonly associated with sequelae secondary to systemic effects of COVID-19 infection as well as primary viral effects on the CNS and peripheral nervous system. Common presentations include encephalopathy with delirium/psychosis, inflammatory CNS syndromes, ischemic strokes, peripheral neurological disorders including Guillain–Barre syndrome, and an/hyposmia and dys/hypogeusia (altered sense of smell and taste) (5, 6, 8–11, 13–16). As with other CNS coronaviral infections, the proposed pathological mechanisms include secondary inflammatory syndromes, secondary immune-mediated syndromes, neurological consequences of systemic disease including sepsis, hypoxia, and hypercoagulability, and direct neuronal/glial cell injury.

TREATMENT

Data relating specifically to treatment of naturally occurring CNS coronavirus infections is extremely limited in humans, domestic, and production animals. Therapeutic approaches are generally similar regardless of organ systems affected; however specific issues relating to the blood–brain barrier/blood–CSF barrier limitations on drug delivery and pronounced neurological effects due to secondary inflammation need to be considered. The variable pathogenesis and clinical aspects of coronavirus disease in non-human species means that translational therapeutic studies in these animals may have some limitations. However, CNS coronaviral infections in domestic cats (FIP), in particular, may be translationally valuable given both the severity of disease presentation and the individualized approach to treatment in a companion vs. production or research setting. Recent data relating to treatment of both non-CNS and CNS FIP with antiviral drugs may have relevance to specific aspects of ongoing trials in SARS-CoV-2 patients. Interestingly, domestic and big cats are susceptible to SARS-CoV-2 infection, consistent with expression of ACE2 viral receptor in these species (87, 88), although associated clinical CNS disease has not been reported (89, 90).

Management of coronavirus infections consists of a variety of preventative and therapeutic approaches based on pathogenic mechanisms of the targeted coronaviruses as well as species-specific aspects of clinical disease. Several reviews of therapeutic aspects of coronavirus infections are available and discuss the main arms of disease management relating to prevention, husbandry, vaccination, antiviral drugs, and modulation of immune/inflammatory aspects of coronavirus infections in humans (91–94) and domestic animals (57, 95–98).

Preventative

Preventative management, beyond husbandry, and environmental management of disease outbreaks is centered around vaccination. The value of vaccination depends on both severity of the disease and efficacy/longevity of the vaccines developed. Development of effective vaccines for human coronavirus infections, particularly SARS-CoV-2 (COVID-19), is an ongoing priority (91, 92). Inactivated and live attenuated vaccines have been shown to provide protective immunity in several domestic species (98); however, the value of vaccination has to be balanced against expense and prevalence of disease. Immunological sequelae following coronavirus infection appears to play a major role in disease progression, particularly in the CNS, and adverse events associated with vaccination must be considered in this context. Immunity to FIP is largely cell mediated, and humoral immunity with systemic antibodies to FIP virus may exacerbate disease by enhancing viral uptake and replication in macrophages and by stimulating a vascular-oriented Arthus-type hypersensitivity reaction (57, 99). An intranasal temperature-sensitive mutant FIP vaccine generating a local IgA response has been shown to have efficacy; however, its value in the clinical setting is questionable (57).

Anti-inflammatory/Immunomodulatory Therapies

Dexamethasone is one of the few therapies that has been shown to have a beneficial effect in COVID-19 patients (100), although the pros and cons of anti-inflammatory vs. immunosuppressive effects have been debated with COVID 19 as with other coronaviruses such as SARS-CoV and MERS-CoV. Use of corticosteroids and intravenous immunoglobulin therapy for non-specific inflammatory and potential immune-mediated aspects of CNS disease have been anecdotally reported in neurological COVID-19 (8). Non-specific anti-inflammatory drugs such as corticosteroids, cyclophosphamide, and cyclosporine have anecdotally been associated with amelioration of signs in FIP CNS disease but are not curative (57, 66, 95–97). More targeted inhibition of specific cytokines such as TNFα have shown mixed therapeutic benefits in systemic FIP (101–103), and poor responses have generally been seen with the use of interferons α, β, and omega (57, 96, 97).

Antivirals—Lessons From Feline Trials

A wide spectrum of antiviral drugs has been developed targeting most aspects of the coronavirus life cycle [reviewed in (92)], including neutralizing antibodies (convalescent plasma or monoclonal), fusion and viral protease inhibitors, nucleoside analogs, host protease and receptor inhibitors, and lipidomic reprogramming drugs. The nucleoside analogs ribavirin, NHC (β-D-N4-hydroxycytidine), and remdesivir/GS-5734 have activity against a variety of RNA viruses including coronaviruses. Chloroquine/hydroxychloroquine is an antimalarial and autoimmune drug that can block viral infection by increasing endosomal pH (required for virus-cell fusion) and can also interfere with glycosylation of cellular receptors. Remdesivir and chloroquine can inhibit SARS-CoV-2 *in vitro* (104) and are in trials for COVID-19 patients. There is currently no evidence for a beneficial effect of chloroquine/hydroxychloroquine in COVID-19 patients (105), and chloroquine had only modest effects in cats with experimentally induced FIP, and toxicity with elevations of serum alanine aminotransferase has been noted (106).

Recent trials using antiviral drugs in clinical FIP have been extremely encouraging that treatment and potential cures are a realistic goal, including for CNS disease. Screening of large numbers of antiviral compounds to identify individual and combinations of drugs shows promise for future effective FIP therapies (107) and may address concerns relating to development of resistance with single drug regimens (108, 109). However, monotherapy with the nucleoside analog GS-441524 (Gilead Sciences Inc.) and a 3C-like antiviral protease inhibitor (Anivive Life Sciences Inc.) have already shown efficacy in experimental and naturally acquired non-CNS FIP (108, 110–112), although limitations associated with drug access across the blood–brain barrier resulted in CNS relapses, particularly with protease inhibitor therapy (108, 112). Cat pharmacokinetic data for GS-441524 showed that CSF concentrations of GS-441524 were ∼20% of plasma levels (111) and that doses five times those shown to effectively treat non-CNS FIP (2–4 mg/kg) would be

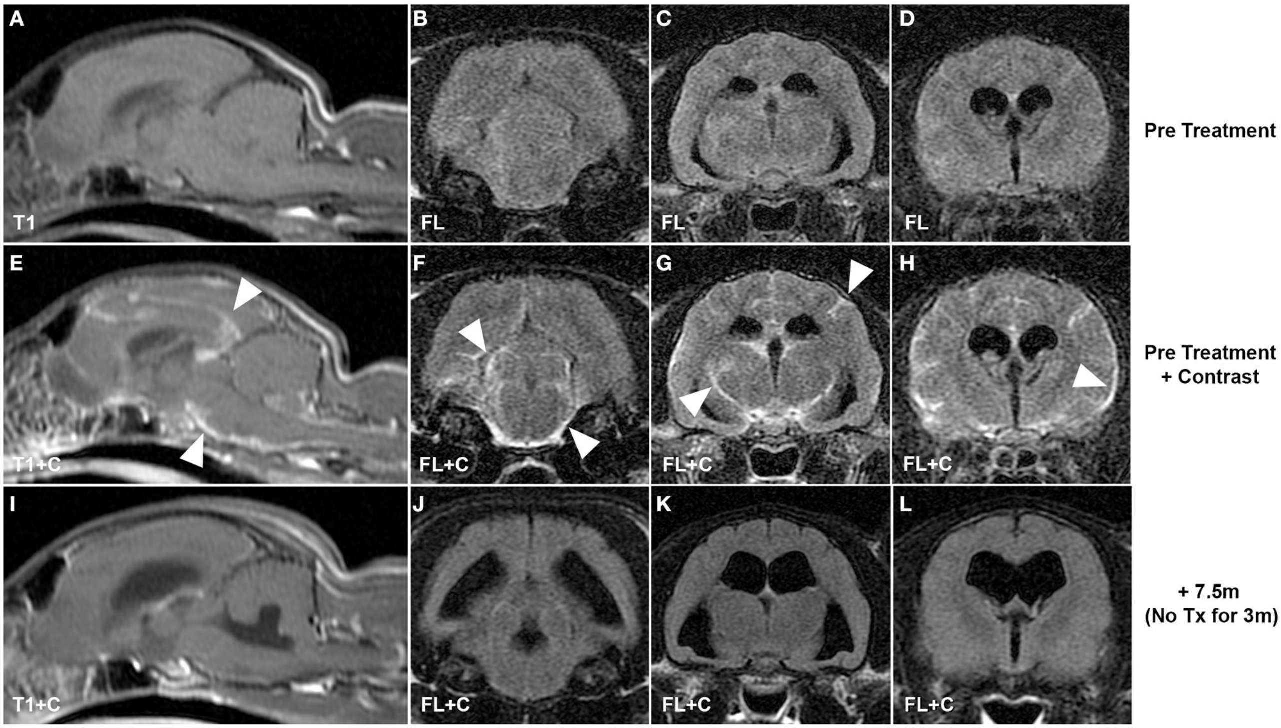

FIGURE 1 | CNS coronavirus infection (FIP) in a cat presenting with neurological deficits and treated with GS-441524, the parent nucleoside of remdesivir. Pre-contrast **(A–D)** and post-contrast T1-weighted and fluid-attenuated inversion recovery pre-treatment MRI sequences **(E–H)** reveal multifocal leptomeningeal lesions (arrowheads) typical of CNS FIP. Resolution of clinical signs was incomplete using drug dosing typically effective in non-CNS disease (4 mg/kg); however, increased dosing (10 mg/kg) resulted in resolution of clinical signs and resolution of MR lesions on images acquired 7.5 months after initiation of treatment and 3 months after completion of treatment **(I–L)**. T1, T1-weighted; FL, fluid-attenuated inversion recovery; +C, contrast (gadopentetate dimeglumine, "Magnevist").

necessary to achieve 1 μM concentrations consistent with the *in vitro* 50% effective concentration (EC_{50}) to prevent coronavirus cytopathic effects. Subsequent pilot data from cats presenting with CNS FIP supported these data with resolution of disease signs and apparent cures with dosing up to 10 mg/kg (**Figure 1**) (113). GS-441524 is a 1′-cyano-substituted adenine C-nucleoside ribose analog that inhibits viral RNA synthesis once it has been tri-phosphorylated intracellularly. Remdesivir (GS-5734) is a monophosphate prodrug of GS-441524 with the phosphate masked by McGuigan prodrug moieties designed to promote release of the monophosphorylated analog intracellularly and to overcome the perceived rate-limiting first phosphorylation step. Remdesivir has been given emergency use authorization for treatment of SARS-CoV-2 with encouraging if limited preliminary results (114–116). Given the efficacy of GS-441524 in the treatment of FIP, it has been suggested that there may be advantages to the use of the parent (GS-441524), rather than the prodrug (remdesivir) in human trials (117). Remdesivir appears to be rapidly metabolized in the serum to GS-441524 rather than entering cells intact (118, 119), and GS-441524 can be present in the serum at concentrations 1,000-fold higher than remdesivir (118). *In vitro* comparison of antiviral efficacy of remdesivir and GS-441524 against SARS-CoV and MERS-CoV showed similar EC_{50} values, and GS-441524 values were lower in some cases than the EC_{50} values reported in feline CRFK cells (Crandel Reese Feline Kidney Cells) infected with FIP virus (109, 111). GS-441524 serum levels in humans would more likely exceed these EC_{50} values based on published data (117), and similarities to cat *in vitro* data together with the encouraging clinical efficacy in cat FIP (111–113) would support the investigation of GS-441524 for use in human coronaviral disease, including CNS infections. Current dosing of remdesivir in COVID-19 trials is 200 mg loading followed by 100 mg (114, 115), equivalent to 1.5–3 mg/kg for a 70-kg human. These doses fall within the range shown to be effective in treating non-CNS FIP in cats (111, 112); however, the increased doses necessary to treat CNS FIP infections (8–10 mg/kg) in cats (113) would be equivalent to 560–700 mg for a 70-kg human. GS-441524 appears to have a high therapeutic index and minimal adverse effects at all doses of GS441524 reported in cats (2–10 mg/kg) (111–113). CNS blood–brain, blood–CSF barrier pharmacokinetic limitations are likely to be similar between cats and humans, and experience with FIP suggests that dose escalation of remdesivir (or GS-441524) may be necessary to optimize clinical efficacy in humans if targeting of coronavirus within the CNS is a specific therapeutic goal.

GS-441524 is not approved or available for clinical veterinary use limiting the potential for expanded and regulated clinical studies necessary to support approval in clinical veterinary practice. Unapproved sources of GS-441524 have become available online to owners of FIP cats, and FIP advocacy groups have collated observational data relating to outcomes in these "owner-treated" animal cohorts. Data arising from unverified drug sources and owner reported outcomes have major limitations; however, against a historical background of almost universal fatality in cases of CNS FIP, some clinically relevant data may be available. Advocacy group treatment regimens, based on published data (111–113), typically recommend a minimum 12-week course of treatment, with 4- to 6-mg/kg doses for non-CNS FIP treatment and 8- to10-mg/kg doses for CNS disease cases. Cure or remission is defined as no evidence of clinical disease >12 or <12 weeks, respectively, after completion of treatment. Data from an FIP advocacy group (personal communication) detailing owner outcomes from 110 cats with neurological signs and presumptive FIP treated with unapproved GS-441524 drug showed the following: 57/110 (52%) in remission, 22/110 (20%) cured, 9/110 (8%) died or euthanized, and 7/110 (6%) with relapsed CNS disease. Fifteen cats (14%) presented with non-CNS disease but relapsed with CNS signs following treatment. Sequential dose data was available for five cats that relapsed with CNS disease; initial doses ranged from 5 to 7 mg/kg, and four of five cats were subsequently cured with one in remission following dose escalation to 10–16 mg/kg. These uncontrolled data are supportive of the efficacy previously documented in four cats treated with GS-441524 (113) and of the necessity of increased dosing for optimal treatment of CNS infections. A striking aspect of GS-441524 treatment of FIP is the dramatic (often <36 h) improvement in clinical signs following adequate dosing (112, 113). Resolution of gross neuropathology in this time period is unlikely, and it is possible that decreased production of inflammatory cytokines, known to be a significant component of CNS coronaviral pathology, may be responsible for this rapid clinical improvement. Whether similar clinical correlates will be present with treatment of human coronaviral infections with GS-441524 or remdesivir remains to be seen.

Naturally occurring coronaviral infections in companion and production animals have many similarities to human pandemic-related diseases such as SARS, MERS, and COVID-19, although species and virus-specific factors described above mean that broad translation of therapeutic data across species will have major limitations. However, findings relating to basic treatment-related factors such as blood–brain barrier effects on therapeutic drug penetration to the CNS are likely to be relevant across species. It is currently unclear to what degree viral infection of the CNS impacts the clinical outcome in COVID-19 patients and how it may influence therapeutic practice; however, advances in the treatment of previously fatal coronavirus infections in cats with antiviral nucleoside analog drugs, particularly in the context of CNS infection, is encouraging that similar approaches may be efficacious in other species.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

PD conceived and wrote the manuscript.

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Reflecting on One Health in Action During the COVID-19 Response

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The COVID-19 pandemic, a singular disruptive event in recent human history, has required rapid, innovative, coordinated and collaborative approaches to manage and ameliorate its worst impacts. However, the threat remains, and learning from initial efforts may benefit the response management in the future. One Health approaches to managing health challenges through multi-stakeholder engagement are underscored by an enabling environment. Here we describe three case studies from state (New South Wales, Australia), national (Ireland), and international (sub-Saharan Africa) scales which illustrate different aspects of One Health in action in response to the COVID-19 pandemic. In Ireland, a One Health team was assembled to help parameterise complex mathematical and resource models. In New South Wales, state authorities engaged collaboratively with animal health veterinarians and epidemiologists to leverage disease outbreak knowledge, expertise and technical and support structures for application to the COVID-19 emergency. The African One Health University Network linked members from health institutions and universities from eight countries to provide a virtual platform knowledge exchange on COVID-19 to support the response. Themes common to successful experiences included a shared resource base, interdisciplinary engagement, communication network strategies, and looking global to address local need. The One Health approaches used, particularly shared responsibility and knowledge integration, are benefiting the management of this pandemic and future One Health global challenges.

Keywords: SARS-CoV-2, One Health, infectious disease epidemiology, collaborative networks, community network integration, knowledge integration

INTRODUCTION

The scope and impact of the COVID-19 pandemic is unprecedented in modern times. At the time of writing, over 10 million confirmed human cases and 0.5 million deaths from SARS-CoV-2 infection have been reported (1), and the global community is facing enormous challenges. In these circumstances, an effective response is complex, requiring coherent and collaborative engagement by multiple stakeholders across a diverse network. In a pandemic, a country on its own has limited possibilities, particularly when dealing with a new threat and limited knowledge of its consequences and how to mitigate it; a linking of national priorities and global disease governance is critical (2). For example, knowledge needs to be shared about effective treatments, disease epidemiology including risk factors, people's reaction to measures and effective testing protocols, among others.

One Health is very relevant to the current pandemic. It is concerned with interactions and dependencies in complex systems and promotes a sustainability-oriented approach of health (3) that brings together natural and social sciences and is characterized by collaboration, participation, sharing and exchange in a framework of knowledge integration in health (4). A key feature is the concept of shared responsibility, with the potential for innovative and non-uniform solutions to manage complex problems (5). For example, shared responsibility is used as a collaborative approach to biosecurity management across multiple stakeholders with diverse and complementary perspectives, knowledge and realities to produce robust and prepared biosecurity systems (6). The management and governance of complex biosecurity issues, including prevention, preparedness, detection, response and recovery, is coordinated and shared across government agencies, industry organizations, users and the broader community (7, 8). A clear definition and shared understanding of the concept, including roles and responsibilities, and a consistent and appropriately resourced coordination throughout the system are needed to form true and effective partnerships (9, 10). A shared responsibility approach, agreed upon during peacetime, could support the management of any complex health issue, such as the COVID-19 pandemic, and be implemented at different levels (local, regional, national and international).

The implementation of a partnership approach does not come without its challenges. Knowledge integration and particularly the sharing of data is impacted by political boundaries, as shown in previous evaluations of One Health initiatives (11). Further, sectoral and disciplinary silos constitute an impediment to the ability of stakeholders to mount a timely and effective outbreak response. In such systems, there is potential to improve the efficiency of information flow and knowledge exchange and integration. Traditionally, in the various health sectors, solutions are often prescribed top-down, implying singular linear pathways in isolated aspects of health, whereas health agency and shared responsibility approaches may be more suitable when dealing with unpredictability, uncertainty, and ambiguity.

A recent promising approach to support such collaborative approaches and implement shared responsibility in practice is called Community Network Integration. It aligns distributed networks under a common leadership and collaborative governance framework including means to identify and engage appropriate expertise, human resources and co-funding in order to execute priority scalable solutions-oriented (pilot) projects. The approach also integrates a systems approach to project management, communication, and data integration as well as novel application of principles of social psychology to engage stakeholders and create a culture of high emotional energy vital to collaboration and creative problem solving (12). Thereby, it operationalises the essential dimensions of One Health that include (1) systemic thinking, (2) holistic planning, and (3) transdisciplinary working, supported by an enabling environment to allow for (4) sharing, and (5) learning, endorsed through (6) a systemic organization (13).

In this article, we use three case studies from different world regions to discuss elements of One Health approaches in the COVID-19 response. The three case studies are based on the authors' experiences and illustrate which of the essential One Health dimensions listed above applied in practice during the crisis. They provide examples of collaboration, shared responsibility and knowledge integration and illustrate opportunities and weaknesses.

CASE STUDIES

Case Study 1: COVID-19 Modeling Support in the Republic of Ireland: A Case-Study of Rapid Response Demonstrating the Value to Utilizing Cross-Disciplinary Actors Toward a Common Goal

In Ireland, the National Public Health Emergency Team (NPHET) was established on 27 January 2020, to provide national direction, support and expert advice on the development and implementation of a strategy to contain COVID-19 (14). The first confirmed COVID-19 case in Ireland was reported on 29 February, the Special Cabinet Committee on COVID-19 was formed on 3 March, and a National Action Plan was published on 16 March.

NPHET was supported by a number of expert groups, including the Epidemiological Modeling Advisory Group (IEMAG), which was established on 7 March [(15); see **Supplementary Figure 1**]. IEMAG was tasked with developing capacity for mathematical modeling (epidemiological, demand/supply, geospatial) to enable real time modeling of COVID-19 in the Irish population, drawing on expertise in relevant disciplines from government agencies and universities throughout Ireland. Here we focus on the epidemiological parameters team within the IEMAG epidemiological modeling subgroup, which was tasked with gathering evidence on key characteristics of COVID-19. An important remit of the team was to link biological understanding with technical quantitative skills to improve the building of mathematical and statistical models and help communicate effectively the findings to NPHET and other stakeholders.

The requirement for a rapid response led to a broad call to action from stakeholders with various expertise to contribute, in some cases beyond the traditional human medical disciplines. The team was chaired by a veterinary epidemiologist, with interdisciplinary membership from human public health, agriculture, veterinary medicine, food safety, disease ecology, and One Health backgrounds. Initial team selection was guided by disciplinary expertise, full-time availability (at short notice) and prior working relationships. The group's diverse interests and skills were well-suited to rapidly gathering evidence, and undertaking quantitative secondary and meta-analyses, in response to the emerging threat (16–22). In the context of IEMAG, the multidisciplinary One Health team were able to ensure that the national mathematical models were underpinned by robust biological understandings, both during model development and evaluation. This was particularly important in the context of model fitting to emerging datasets, where the evidence base, and basic understanding of the epidemiology of the pathogen, was rapidly changing. Due to the rapid and changing needs of modelers, the composition and focus on tasks by the subgroup was dynamic, with members requiring to pivot from one parameter to another. In addition, the expertise and experience of the national Health Information and Quality Authority (HIQA), and researchers with particular skills (e.g., virology) were sought and contributed to the network, as required. Throughout, advice from international expertise (e.g., World Health Organization, European Center Disease for Disease Prevention and Control) were monitored and incorporated into IEMAG's work.

In terms of lessons learned, the rapid community-based aggregation of skills applied to a single acute problem should be held as an exemplar of how a distributed network of expertise can contribute in an efficient and effective way toward a goal. Interdisciplinary synergies were central to progress, both between mathematics and the life sciences and, importantly, between medical and allied disciplines. One Health perspectives predominated and there was cross-pollination of ideas and skills across disciplines to achieve efficiencies and better, more dynamic, systems. Challenges included remote working while maintaining communication and ensuring there was no duplication of effort across various NPHET subgroup teams. Furthermore, given the finite resources available, the COVID-19 response led to a temporary diversion of expertise and resource from other aspects of national animal health management. This case study is an important example of new thinking, diversity of thought, and new networks of expertise within Ireland.

Case Study 2: A State Level One Health Approach to Respond to COVID-19: Perspectives From the New South Wales Department of Primary Industries

On 21 January 2020, the Australian Chief Medical Officer (CMO) issued a determination adding "human coronavirus with pandemic potential" to the Biosecurity (Listed Human Diseases) Determination 2016. As a result, the Australian Health Protection Principal Committee, the key decision-making committee for health emergencies formed by the CMO and state and territory Chief Health Officers, was convened and daily meetings activated. In addition, national coordination was also activated for responding to the health emergency through the National Incident Room, the strategic reserve of personal protective equipment through the National Medical Stockpile and the provision of clinical and academic leadership through the National Trauma Center. Meetings of state, territory and Commonwealth health ministers to discuss pandemic readiness also started. On 25 January, Australia reported its first case of COVID-19, and the Australian Health Sector Emergency Response Plan for Novel Coronavirus (COVID-19 Plan) was implemented on 7 February (23). The COVID-19 Plan acknowledges that the primary responsibility for managing the impact of the outbreak lies with the state and territory governments (24). In New South Wales (NSW), the NSW State Emergency Management Plan (EMPLAN) and the NSW Human Influenza Pandemic Plan (sub-plan to EMPLAN) were implemented (24, 25).

Early in the response, a One Health approach was implemented through the collaborative engagement of animal health experts, including veterinarians and epidemiologists, from NSW Department of Primary Industries (DPI) and other institutions (e.g., universities, consultants), sharing expert knowledge. This approach is pre-defined by EMPLAN, under which a Combat Agency is nominated to lead operations (in this case, the Ministry of Health) and able to request support from other government areas, such as the NSW DPI. Animal health specialists worked for the Public Health Emergency Operations Center, responsible for activities such as tracing, research and providing expert advice, in the epidemiology and tracing units. In addition, the Ministry of Health liaised with other government agencies to establish remote tracing capabilities, including sharing of databases, online training and debriefs (due to the travel limitations) and the need to increase contact tracing capacity. As the responsible agency for providing agriculture and animal support during emergencies (under EMPLAN), NSW DPI as the Agriculture and Animal Services Functional Area was present within the State Emergency Operations Center throughout the response, liaising with health services with respect to animal care. Furthermore, the NSW state animal laboratory provided diagnostic services to NSW Health. NSW DPI worked with Australia's Animal Health Committee (AHC) to develop science-based, nationally consistent policy on animal health issues related to COVID-19, and supported the agriculture and animal sectors in achieving continuity of their businesses to safeguard animal health and welfare and help ensure a secure food supply (26). AHC developed and implemented policies, operational strategies, risk assessments and communications around SARS CoV-2 and animals and managing Emergency Animal Diseases (EAD) during human pandemics.

As key learning of this response, COVID-19 highlighted the importance of a well-resourced response using a One Health approach, involving a broad range of human and animal health stakeholders and shared resources, which could then be scaled back as needed. The COVID-19 situation also highlighted the need for appropriate communication and management of animal health and welfare during human pandemics.

Case Study 3: One Health in Action: Experiences From the Africa One Health University Network (AFROHUN) COVID-19 Knowledge Sharing Response

The Africa One Health University Network (AFROHUN), formerly One Health Central and Eastern Africa (OHCEA) is a University led network of 24 public health, veterinary medicine, pathobiology and environmental health institutions and 16 universities in eight countries in East, Central and West African regions (Cameroon, Democratic Republic of Congo, Ethiopia, Kenya, Rwanda, Senegal, Tanzania, and Uganda). Since its inception in 2010, AFROHUN supports institutional changes in teaching and learning environments in higher institutions that promote One Health approaches.

In the absence of a global workforce, most African national COVID-19 response actions relied on national health professionals to provide the much-needed workforce in the management of the pandemic. Universities were among the key institutions that supported different national response task forces. University members served on scientific task forces with evidence-based and science-based data shaping response strategy options as the mainstream health workforce within ministries were at the forefront of the response.

Between 23 March 2020 and 18 June 2020, AFROHUN through its wide continental network in collaboration with the USAID-funded One Health Workforce – Next Generation (OHW-NG) consortium led by University of California, Davis, provided a platform where network members (faculty and students), practitioners in One Health, and stakeholders virtually via ECHO (Extension for Community Healthcare Outcomes[1]) sessions twice a month accessed the current information on COVID-19 as it evolved. Expert presentations were made by global and in-country teams and real issues and dynamics experienced during response actions were discussed in an interactive way. Selected topics for discussions were delivered over three months by experts in infectious disease epidemiology, human medicine, public health, environment and occupational health, veterinary medicine, immunology and molecular biology, among others, working at the forefront of the response at country, regional and global levels. This provided expert knowledge and experiences on COVID-19 to faculty and practitioners during the webinars. The knowledge gained from the webinars was appreciated by participants, some of whom used it in their different roles in national COVID-19 response teams while a number of faculty indicated readiness to use the rich knowledge in their classes when teaching students. The sessions were perceived to provide valuable knowledge that participants used in their national duties on different COVID-19 task forces, as illustrated by these quotes:

"*During this period, we were discussing options to reshape response measures in the surveillance commission because in Kinshasa capital city cases were still rising. At that time, the herd immunity theory that was discussed during the AFROHUN COVID-19 session on immunity issues and interventions for COVID-19. We learned more about it and about the advances in vaccine development. This improved my knowledge, which I shared, and helped us to focus on improving our testing capacities, as there is no evidence supporting such a theory*." Dr. Marc Yambayamba, AFROHUN country manager in DRC, member of the national COVID-19 surveillance team.

"Based on knowledge we have gained on multidisciplinary approaches in addressing health issues, we mobilized students into One Health Student Club (SOHIC) and we have been active in COVID-19. The club, a multidisciplinary team of students from Makerere University and Mbarara University of Science and Technology in Uganda have been raising awareness about COVID-19 to communities and providing mental health support." Muganzi David Jolly, President, Students One Health Innovation Club, Mbarara University of Science and Technology, Uganda.

"I was asked to lead a team that was responsible for advising the government on the design and necessity for wearing cloth face masks in crowded places such as bus stands, markets, hospitals and places of warship. Now mask use is widespread as one of the preventive actions against COVID 19. In my leadership role, I have used some of the ideas from the AFROHUN ECHO sessions." Prof. Japhet Killewo, Professor of Epidemiology at Muhimbili University of Health and Allied Sciences (MUHAS), Tanzania.

An AFROHUN internal review identified several lessons learnt from the three months of COVID-19 sessions. The power of existing platforms, strong leadership, the combination of global and in-country perspectives and the ability of leveraging networks was highlighted, with around 200 participants and experts being part of the sessions, providing valuable multi-disciplinary, global and local in-country perspectives. The tight schedules of the task force members at the frontline of the pandemic prevented engagement of mainstream ministries in the design of the sessions. Participation of representatives from government and members from different COVID-19 task forces helped bridge this gap. Their perspectives on the issues and dynamics of the pandemic helped to shape subsequent sessions. A more efficient information flow in the national response system to reach diverse users could have enhanced the design and delivery of the sessions. Official engagement of specific task forces such as the scientific committees on the ECHO sessions could have added value.

DISCUSSION

The three case studies each demonstrate important benefits from the use of One Health approaches in the management of the COVID-19 pandemic. The sharing of resources, multidisciplinary engagement and communication network strategies were common across the three case studies, in support of knowledge integration and more effective response management. Each can be placed within a One Health framework (13), providing examples of an effective engagement of expertise and in-kind resources (e.g., labor, connectivity, materials) from a broad range of relevant stakeholder groups. Moreover, they illustrate One Health approaches within inclusive national and local outbreak teams, including transparent use of information, multi-way dialogue, information sharing, and the development of solutions through collaborative learning.

With regards to the six One Health dimensions that are described at the beginning of the paper, the three case studies all had clear sharing and learning structures in place that facilitated an exchange of data, information, and knowledge,

[1]ECHO model^{TM}, https://echo.unm.edu/about-echo/model/

as well as accessing and generating new knowledge through collaborative processes. All case studies described working across disciplines, but remained within the boundaries of the natural sciences and did not engage either the social sciences or the humanities. Also, wider society engagement was lacking, which meant that collaborative working remained within the multi- and interdisciplinary spheres and did not reach transdisciplinary working. Holistic planning was a key feature of case study 2, which provided a strong basis for the actions implemented. Systemic organization was dominant for AFROHUN, with the existence of a large, formal network of universities that allowed prompt recruitment of scientific experts into the response. None of the case studies explicitly described systemic thinking even though it is advocated by the WHO (27) and the Association of Schools and Programs in Public Health (28, 29). These case studies were conducted during emergency situations where rapid and unequivocal instructions and responses are demanded. In contrast, system thinking requires that the problem is adequately formulated, the right stakeholders are selected, a vast set of problem-solving options are considered, boundaries are defined correctly, the approach is systematic rather than focussed, and connections are not ignored. Given the need for rapid responses, the resulting "messiness" introduces uncertainty, and may unearth conflicts in ethics, values, judgement and background experiences. In addition, perspectives may change due to system dynamics which pose additional challenges to public communication (30). This may emphasize that these debates must take place as part of the preparedness process if they should be operational in an emergency situation.

The case studies have demonstrated how expertise can be mobilized and shared quickly, given appropriate support infrastructure and in the light of the pressing needs of the pandemic. It is hoped that lessons learned can be extended to "peacetime," outside the crisis. Interdisciplinary synergies, underpinned by One Health concepts, will also be needed to manage critical global challenges, including those relating to climate change and antimicrobial resistance (31). To harness both the power of new thinking and networks of expertise, it is recommended that preferred solutions are supported by effective network-wide business systems (e.g., management, financial, communications, IT, and human resources) and dynamic learning facilities conducive to transparent knowledge and data sharing, dialogue and innovation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BH, AB, and MH-J conceived the study. AB and SM wrote the case study 1 (Ireland). MH-J and OS wrote the case study 2 (NSW, Australia). WB and AY wrote the case study 3 (AFROHUN). All authors contributed to developing, writing, editing of the paper, and approved the manuscript for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.578649/full#supplementary-material

Supplementary Figure 1 | Overview diagram of the structure of the National Public Health Emergency Team (NPHET), including the broad stakeholder composition demonstrating the interrelationship between government, public health authorities, and academia in response to the COVID19 epidemic in Ireland. CMO, Chief Medical Officer.

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Bovine Interferon Lambda Is a Potent Antiviral Against SARS-CoV-2 Infection *in vitro*

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Interferon lambda (IFN-λ) is an antiviral naturally produced in response to viral infections, with activity on cells of epithelial origin and located in the mucosal surfaces. This localized activity results in reduced toxicity compared to type I IFNs, whose receptors are ubiquitously expressed. IFN-λ has been effective in the therapy of respiratory viral infections, playing a crucial role in potentiating adaptive immune responses that initiate at mucosal surfaces. Human IFN-λ has polymorphisms that may cause differences in the interaction with the specific receptor in the human population. Interestingly, bovine IFN-λ3 has an *in silico*-predicted higher affinity for the human receptor than its human counterparts, with high identity with different human IFN-λ variants, making it a suitable antiviral therapeutic candidate for human health. Here, we demonstrate that a recombinant bovine IFN-λ (rbIFN-λ) produced in HEK-293 cells is effective in preventing SARS-CoV-2 infection of VERO cells, with an inhibitory concentration 50% (IC50) between 30 and 50 times lower than that of human type I IFN tested here (α2b and β1a). We also demonstrated the absence of toxicity of rbIFN-λ in human PBMCs and the lack of proinflammatory activity on these cells. Altogether, our results show that rbIFN-λ is as an effective antiviral potentially suitable for COVID-19 therapy. Among other potential applications, rbIFN-λ could be useful to preclude virus dispersion to the lungs and/or to reduce transmission from infected people. Moreover, and due to the non-specific activity of this IFN, it can be potentially effective against other respiratory viruses that may be circulating together with SARS-CoV-2.

Keywords: COVID-19, bovine IFN-λ, antivirals, respiratory viruses, biotherapeutic agent

INTRODUCTION

Interferons (IFNs) are antiviral cytokines produced by almost any cell type upon recognition of viral molecular patterns and constitute the first line of defense against viral infections. Two types of IFNs are produced during the innate phase of the immune response: type I IFNs (13 subtypes of IFN-α, IFN-β, IFN-ε, IFN-k, and IFN-ω in humans) and type III IFNs (4 subtypes: IFN-λ1 or IL-29, IFN-λ2 or IL-28A, IFN-λ3 or IL-28B, and IFN-λ4 in humans) (1). These IFNs bind to specific receptors on target cells and initiate similar but non-redundant signaling pathways that lead to the expression of IFN-stimulated genes (ISGs) (2, 3). Proteins produced from those ISGs trigger an anti-viral state in the target cells that directly interfere with different steps of viral replication and indirectly modulate the host-immune response to virus infection (4–7). Due to their biological activity, IFNs have been studied or tested as therapeutic tools in the treatment of emerging and reemerging coronaviruses and other viral infections for which no approved drugs or vaccines are available (8–11).

The main difference between both IFN types is the location of their receptors. Type I IFNs recognize specific receptors that are ubiquitously expressed on the surface of all nucleated cells. Consequently, the clinical use of these molecules frequently causes side effects including fever, fatigue, and malaise mainly due to systemic proinflammation elicited on non-target cells (12, 13). Conversely, IFN-λ signals through the engagement of a heterodimeric receptor complex IFNLR1/IL10Rβ (IFNLR) whose expression is restricted to cells and tissues of epithelial origin, including epithelial cells of the respiratory and digestive tracts (1, 14). Due to the IFNLR location, IFN-λ constitutes the first line of defense controlling virus infection at the site of entry.

The COVID-19 pandemic has led to reconsider the use of available antivirals, and among them, IFNs. The use of IFNs is supported by the fact that SARS-CoV-2 induces a very weak endogenous expression of IFNs in infected cells (15–17) that may hamper the early innate immune response after infection. Hence, the use of exogenous IFNs, either for prophylaxis or early therapy to stimulate antiviral immunity, might be successful for treating COVID-19 (18, 19). In this context, IFN-λ has arisen as a promising candidate due to its localized activity on epithelial cells of the respiratory tract, which may reduce side effects and inflammation associated with the systemic action of type I IFNs.

One of the limitations of using human IFN-λ as a universal therapeutic molecule resides in the fact that it has several genetic variants (20, 21) that might have different stability and affinity in the interaction with the IFNLR. Engineering of IFN-λ to assess natural or *in silico* predicted mutations critical to maintaining the antiviral activity proved that the strength of the interaction of between IFN-λ and its receptor could modulate downstream functions (22–26). The strength of this interaction may modify the expression of the ISGs involved in the response to SARS-CoV-2 infection and even the virus receptor (ACE 2) on epithelial cells (27), promoting the reduced IFN signaling in infected cells. Seeking for an innovative high-performance low-cost IFN-λ for use in human health therapy, we developed a recombinant bovine IFN-λ expressed in HEK-293 cells (rbIFN-λ) hypothesizing that an enhanced binding capacity to the human heterodimeric receptor complex will improve its antiviral efficacy.

We have recently demonstrated that rbIFN-λ can activate the human Mx-promoter and that it has an effective antiviral activity *in vitro* against vesicular stomatitis virus (VSV), foot-and-mouth disease virus (FMDV), and bovine viral diarrhea virus (BVDV) (28). Moreover, treatment of calves with rbIFN-λ protected these animals from the disease caused by BVDV, downregulated the proinflammatory response, and promoted the development of the adaptive immune response (29). Here, we assessed for the first time the antiviral activity of this rbIFN-λ against SARS-CoV-2 *in vitro* and its safety on human immune cells. The affinity of bIFN-λ for the human receptor was also analyzed and compared to that of its human counterparts, following different *in silico* approaches.

MATERIALS AND METHODS

Cells and Virus

HEK-293 cells were provided by the Argentinean Cell Bank at INTA and VERO-E6 cells by the Servicio Cultivos Celulares, INEI-ANLIS "Dr. Carlos G. Malbrán." MDBK-t2 cells (30) were kindly provided by Dr. Bryan Charleston (The Pirbright Institute). Cell lines were maintained in Earle's Minimum Essential Medium (EMEM) containing 10% fetal bovine serum (FBS; Internegocios, Argentina), 2 mM L-glutamine, 1 mM sodium pyruvate, 1,500 mg/L sodium bicarbonate, 15 mM HEPES, and a commercial solution containing streptomycin (10 μg/ml), amphotericin B (0.025 μg/ml), and penicillin (10 UI/ml) at 37°C, 5% CO_2. VERO cells cannot produce IFNs, but can respond to exogenous treatment (31).

Peripheral blood mononuclear cells (PBMCs) were purified from heparinized blood from two different volunteers using Histopaque® 1083 (Sigma-Aldrich, Thermo Fisher, DE USA) centrifuged at 1,000 × *g* for 30 min. A written informed consent was obtained from each peripheral blood donor, and procedures were in accordance with the 1964 Declaration of Helsinki and its later amendments and approved by National Ethics Committee of Buenos Aires Province through ACTA-2020-16644926-GBEBA-CECMSALGP.

A local strain of SARS-CoV-2 isolated from a clinical sample positive for COVID-19 in Buenos Aires, Argentina was used in this study. This strain was *in vitro* characterized by staff of the "Servicio Virosis Respiratorias INEI-ANLIS-Malbrán," verifying its cytopathic effect (CPE) on VERO cells. Its whole genome was also sequenced (GISAID accession numbers EPI_ISL_420600). Viral stock was produced by infecting VERO cells and titrated following standard procedures. Briefly, serial 10-fold dilutions of the viral stock were plated in sextuplicate, and after 48–72 h of incubation at 37°C, the number of wells showing CPE was recorded. Viral titers were estimated using the Reed and Müench method and expressed in tissue culture infective dose 50% ($TCID_{50}$)/ml (32).

Recombinant Bovine IFN-λ

Details of sequence, cloning, and expression of the rbIFN-λ (bovine IFN-λ3, GenBank accession number HQ317919.1) have already been published (28). The batch used in this study was produced in HEK-293 cells and quantified in a reporter system using MDBK-t2 cells stably transfected with a construct that contains the human promoter of the MxA gene upstream of a reporter gene, chloramphenicol acetyltransferase enzyme (CAT) (30). Units of biologically active bovine rIFN-λ were measured by MxA-CAT ELISA as previously described (33) with some modifications. Briefly, MDBK-t2 cells were seeded into 12-well tissue culture plates at a density of 5×10^5 cells/well. After 24 h of incubation at 37°C and 5% CO_2, the culture medium was replaced with 500 μl of medium containing 250 μl of different dilutions of the rbIFN-λ preparation. Following a 24-h incubation, cells were washed with cold PBS 1×, lysed for 20 min in lysis buffer, and CAT expression was determined from the cell extracts by CAT ELISA kit (Roche Applied Sciences, IN, USA) following the manufacturer's instructions. Units of antiviral activity per milliliter of the samples were calculated from a standard curve using recombinant bovine IFN-α (from 0.3 to 5.0 IU/ml). The batch produced for this study contained 45 IU/ml of active rbIFN-λ. Recombinant human interferons (rhIFNs) α2b and β1a were kindly provided by Biosidus S.A. (Buenos Aires, Argentina) and contained 3 and 24×10^6 IU/ml, respectively.

In silico Analyses: Modeling and Docking

The sequences of bovine IFN-λ3 and human IFN-λ1, 2, 3, and 4 were retrieved from the GenBank and aligned for identity and similarity, identifying conserved critical regions (34).

Two different *in silico* approaches were used to predict the affinity of bIFN-λ for the human receptor. Using the crystallized ternary complex (hIFN-λ3/IFNLR) structure (PDB accession number 5T5W), a protein structural modeling was performed based on the amino acid sequences of human IFN-λ1, 2, and 3 and bovine IFN-λ3 (SWISS MODEL software; https://swissmodel.expasy.org/). This modeling allowed us to visualize the predicted interaction in the receptor pocket. Each IFN-λ variant was guided by distance restrictions between the Cα atom in contact between the ligand and the receptor and docked into either the structure of IFNLR1/IL10Rβ receptor or the IFNLR1 monomer alone (from PDB) using HDOCK server (http://hdock.phys.hust.edu.cn). After the docking was completed, we identified the 10 structures that yielded the lowest docking free energy for each IFN-λ and selected the one with the lowest root-mean-square deviation (RMSD) against the natural ligand. UCSF Chimera software was used to visualize the models. The dissociation constant (K_d) and free Gibbs energy of binding (ΔG_{bind}) were then estimated (Prodigy server https://bianca.science.uu.nl//prodigy/).

Using the hIFN-λ3/IFNLR complex structure, the interface residues between hIFN-λ3 and each subunit of the heterodimeric receptor were determined using PDB SUM database (35). This crystallographic structure (5T5W) is already an IFN-λ3 mutant (mut-hIFN-λ3) conceived to improve the binding affinity for its receptor (Mendoza 2017). Mutation on the interface residues of the mut-hIFN-λ3 was incorporated using FoldX software (Schymkowitz 2005), creating new variants with replaced interface residues present in hIFN-λ3 or bIFN-λ3, and the ΔG_{bind} of the interaction of the ligand–receptor complex was estimated. Mutant structures were visualized using VMD software (36).

Viability Assessment

The metabolic activity of VERO cells and PBMCs pretreated with 4.5, 9, and 18 IU/ml of rbIFN-λ was measured with TACS® XTT Cell proliferation Assay Kit (TREVIGEN, Gaithersburg, MD, USA) according to the manufacturer's instruction and as previously reported (37). OD values for mock-treated cells were computed as reference of viable cells. Control dead cells were obtained by performing an osmotic shock, incubating the cells overnight (ON) with PBS. Percentage of living cells was referred to values of untreated control wells. Samples were run in triplicate.

PBMCs were also stained with a LIVE/DEAD™ Fixable Dead Cell Stain Kit (Thermo Fisher), according to the manufacturer's recommendations. Fluorescence intensity was determined by FACS analysis at 665 nm (BD Biosciences FACSCalibur™), and results were analyzed using a specific software (FlowJo V10; BD, OR USA).

Cytokine Responses

Heparinized whole blood samples from two different donors were incubated at 37°C and 5% CO_2 with LPS (20 ng/ml, Sigma Aldrich–Thermo Fisher); rbIFN-λ (5 IU/ml) or both rbIFN-λ and LPS were mock treated. After 24 h of incubation, plasma samples were separated by centrifugation (1,200 × *g*, 10 min) and tested for IL-6 and IL-10 production by a chemiluminescent assay at a private clinical laboratory (IACA Laboratorios, Argentina).

Antiviral Activity Against SARS-CoV-2

VERO cells were seeded into 96-well tissue culture plates (1.5×10^4 cells per well) 24 h prior to treatment with serial dilutions (0.0175 to 18 IU/ml) of rbIFN-λ and recombinant human IFN-α2b and IFN-β1a (rIFN-α and rIFN-β, respectively), kindly provided by Biosidus SA. (Argentina), as control treatments. After an ON incubation, the supernatants were removed and cells were infected with SARS-CoV-2 at a MOI of 0.5 in infection medium (as it was previously described but containing only 2% FBS) for 1 h. Medium containing the inoculum was removed and replaced with 200 μl per well of fresh medium (2% FBS) supplemented with the corresponding rIFN at the indicated concentrations or medium alone. Plates were incubated for 48 h, when infected cell control wells showed CPE. At this time point, cell supernatants were collected, pelleted for 10 min at 6,000 × *g* to remove debris, and then transferred to sterile collection tubes for RNA extraction. The cell monolayers were stained with crystal violet, and the resulting OD read at 575 nm in a microplate reader (Synergy H1, BioTek, USA). These results were used to calculate the corresponding IFN concentration that provided 50% of protection to the infection of the cells in culture (inhibitory concentration 50, IC_{50}). Triplicate wells containing IFN-treated non-infected cells were run in parallel as toxicity controls in every experiment.

Detection of SARS-CoV-2 Using a TaqMan qRT-PCR Assay

The antiviral activity of the rbIFN-λ in VERO cells with the SARS-CoV-2 was also assessed by detecting viral genome in cell culture supernatants through an optimized qRT-PCR assay. Briefly, 140 μl of cell culture supernatants seeded in quadruplicates was processed to extract total RNA using the QIAamp Viral RNA Mini Kit (Qiagen, Germany). Reverse transcription and amplification of SARS-CoV-2 E-gene were performed using the Lightmix Modular SARS-CoV (COVID-19) (TIB MOLBIOL-Roche, Switzerland) and the SuperscriptTM III Platinum OneStep qRT-PCR kits (Invitrogen, Thermo Fisher) and run on an ABI 7500 Real-Time PCR System (Applied BioSystems, Thermo Fisher) following standard procedures.

Reverse transcription was done at 50°C for 10 min, followed by a polymerase activation and target denaturation step at 95°C for 10 min, and PCR amplification was run at 95°C for 15 s and 58°C for 35 s (45 cycles). All reactions were performed in a final volume of 25 μl, containing 5 μl of total RNA. A reference curve built upon serial dilutions ranging from 6×10^{-1} to 6×10^{6} copies/μl was used to calculate the number of genome copies in each sample, using standards provided by the Pan American Health Organization (SARS-like Wuhan, Iv-RNA E gene standard 1×10^{8} copies/μl and SARS-like Wuhan, Iv-RNA RdRP gene standard, 1×10^{8} copies/μl). The reduction of the number of SARS-CoV-2 genome copies was also used to estimate IC_{50}, as described for the cell monolayer staining method.

As for the previous section, all experiments involving infective SARS-CoV-2 were performed by the staff of the "Servicio Virosis Respiratorias INEI–ANLIS Dr. Carlos G. Malbrán" at the ANLIS "Dr. Carlos G. Malbrán" BSL-3 facilities.

Statistical Analysis

The standard curve used to estimate viral RNA quantities was run in triplicate and analyzed using GraphPad Prism 9. Results obtained for antiviral activity against the different IFN concentrations were compared using one-way ANOVA Kruskal–Wallis test, followed by Dunn's multiple comparison test. Normal distribution of these values was previously confirmed using the D'Agostino-Pearson normality test (GraphPad Prism 9). The confidence interval used was 95% or 99% depending on the experiment.

RESULTS

Interaction of rbIFN-λ With Human Receptors

There are four human IFN-λ coding sequences clustered at chromosome 9: IFN-λ1 (IL29), IFN-λ2 (IL28A), IFN-λ3 (IL28B), and IFN-λ4. Identity between the amino acid sequences of human IFN-λ was first analyzed (**Table 1A**). The highest degree of identity was found between human IFN-λ3 and IFN-λ2 (96%), followed by the comparison to IFN-λ1 (80%). Identity between human IFN-λ1 and λ2 was 71%, while IFN-λ4 was very different to all the other human IFN-λ (identities <30%). We then compared human IFN-λ1 to IFN-λ4 with the sequence of the rbIFN-λ. Interestingly, the percentage of identical residues were equivalent when compared to human IFN-λ1, 2, and 3 sequences (between 64 and 68%) as well as the similarity that ranged between 74 and 75% (**Table 1B**). As expected from the comparison among human IFN-λ, both the identity and similarity between the rbIFN-λ and hIFN-λ4 were much lower (30 and 43%, respectively). Due to its differences with the other IFN-λ variants under study (both human and bovine), the hIFN-λ4 was excluded from further analysis.

To the best of our knowledge, the potential antiviral activity of bovine IFN-λ on human cells has never been assessed. An *in silico* analysis was first performed to predict the tridimensional structure of the interaction between the bIFN-λ and the human receptor (IFNLR). A protein structure was modeled using the amino acid sequences of the bIFN-λ and the hIFN-λ1, 2, and 3, and the crystal structure of the human IFN-λ3/IFNLR complex was used as template. With these models, PDB files were generated and run in a docking software to visualize the predicted interaction in the receptor pocket, where IFN-λ binds to trigger the JAK/STAT pathway. Both human and bovine IFN-λ exhibited similar secondary and tertiary structures, thus suggesting that they may interact similarly with the IFNLR (**Supplementary File 1**).

The interaction between IFNLR and each modeled IFN-λ was studied in terms of stability through a docking assessment. The free ΔG_{bind} and the K_{d} for the best model generated by the docking procedure were computationally estimated. As it is shown in **Table 2A**, the bovine IFN-λ3/IFNLR prediction yielded the lowest ΔG_{bind} and K_{d} values, suggesting a more stable

TABLE 1 | Analysis of bovine and human IFN-λ sequences.

	hIFN-λ2	hIFN-λ3	hIFN-λ4
A. Identity between human IFN-λ			
hIFN-λ1	139/196 (71%)	153/189 (80%)	54/190 (28%)
hIFN-λ2	–	188/196 (96%)	44/171 (26%)
hIFN-λ3	–	–	45/175 (26%)
	Identities	**Similarities**	**Expect**
B. Identity and similarity between bovine and human IFN-λ			
hIFN-λ1	111/174 (64%)	131/174 (75%)	5e−74
hIFN-λ2	131/198 (66%)	148/198 (74%)	8e−84
hIFN-λ3	134/198 (68%)	149/198 (75%)	2e−86
hIFN-λ4	48/160 (30%)	70/160 (43%)	4e−11

***(A)** Identity of the amino acid sequences between human IFN-λ1 and human IFN-λ4. **(B)** Identities, positives (similarity), and E-values of the alignments between human IFN-λ1 and human IFN-λ4 and the rbIFN-λ sequence.*

TABLE 2 | Interaction with the human IFNLR.

Docking	ΔG_{bind} (kcal/mol)	K_{d}
A. Predicted stability values from IFN-λ/IFNLR interaction		
hIFN-λ1/IFNLR	−12.3	9.30E−10
hIFN-λ2/IFNLR	−12.4	8.30E−10
hIFN-λ3/IFNLR	−13.1	2.30E−10
bIFN-λ/IFNLR	−13.9	6.90E−11
ID	**ΔG_{bind} (kcal/mol)**	
B. Stability values from *in silico* mutagenesis		
WT hIFN-λ3/IFNLR	−36.9141	
bIFN-λ/IFNLR	−38.6697	
mut-hIFN-λ3/IFNLR	−39.0803	

***(A)** The interaction between IFNLR and each modeled IFN-λ was studied in terms of stability through a docking assessment. The free Gibbs energy of binding (ΔG_{bind}) and the dissociation constant (K_d) were computationally estimated. **(B)** An in silico mutagenesis analysis was performed using FoldX software by replacing the interface residues present in both the wild-type hIFN-λ3 and in bIFN-λ. The free Gibbs energy of binding (ΔG_{bind}) of the interaction of the ligand–receptor complex is depicted. hIFN-λ1–3: human IFN-λ1 to 3; bIFN-λ: bovine IFN-λ; WT hIFN-λ3: wild-type human IFN-λ3; mut-hIFN-λ3: mutant human IFN-λ3; IFNLR: human IFN-λ receptor.*

interaction between the bIFN-λ and the IFNLR compared to the human IFN-λ. The highest binding stability of bovine IFN-λ was also observed in the interaction with the monomer IFN-λR1 (data not shown).

Based on the crystallographic structure of the hIFN-λ3/IFNLR complex, interface residues were identified (**Figure 1**). Some of them had been mutagenized previously to obtain the crystal structure (25). The impact of these residues present in both wild-type human and bovine IFN-λ3 on the stability of the interaction with IFNLR was assessed by an *in silico* mutagenesis analysis. These interface residues present in the mut-hIFN-λ3 were replaced by the bovine and wild-type IFN-λ3 amino acids and fitted within the hIFN-λ3/IFNLR structure. The ΔG_{bind} of the interaction was determined (**Table 2B**). The mutations performed on the PDB structure of mut-hIFN-λ3 were H95N, R15Q, H91L, D87E, and D73E (**Figure 1**, center), and K24R, F146L, A150T, and N154 (**Figure 1**, right), based on the amino acid residues present in bIFN-λ. According to ΔG_{bind} values, bovine IFN-λ3 showed higher affinity for the IFNLR than human wild-type IFN-λ3, and the interface amino acids of the bovine sequence may be responsible for this increased interaction efficacy.

Safety of rbIFN-λ

In order to be used as a human therapeutic agent, rbIFN-λ must be safe for human cells and unable to upregulate proinflammatory cytokines in immune cells.

In a first experiment, PBMCs from two different healthy donors were incubated ON with 4.5, 9, or 18 IU/ml of rbIFN-λ, stained with a specific marker to differentiate between live and dead cells and analyzed by FACS (**Supplementary File 2**). Viable and dead cells were quantified as a whole and by gating events according to their size and granularity to identify lymphocytes, granulocytes, and monocytes. No differences were recorded in the number of dead and live cells associated to the increasing concentrations of rbIFN-λ assessed. Mortality rate yielded values below 1% for all samples, even when 18 IU/ml of rbIFN-λ

TABLE 3 | Bovine rIFN-λ is safe for human immune cells.

		Treatment			
		Mock	rbIFN-λ (4.5 IU/ml)	rbIFN-λ (9 IU/ml)	rbIFN-λ (18 IU/ml)
A. Percentage of dead cells					
DONOR 1		0.82 ± 0.11	1.01 ± 0.99	0.74 ± 0.37	0.72 ± 0.38
DONOR 2		0.58 ± 0.29	0.41 ± 0.08	0.98 ± 0.55	0.90 ± 0.42
B. Percentage of total cells					
Donor 1	Granulocytes	24.5 ± 0.92	26.4 ± 1.62	26.4 ± 0.62	24.0 ± 1.93
	Monocytes	4.66 ± 0.15	5.56 ± 0.51	5.32 ± 0.64	4.82 ± 0.10
	Lymphocytes	58.4 ± 1.45	53.0 ± 1.07	56.0 ± 2.83	57.7 ± 2.06
Donor 2	Granulocytes	43.9 ± 1.9	45.5 ± 1.6	42.3 ± 1.9	41.5 ± 3.6
	Monocytes	3.70 ± 0.99	3.57 ± 1.2	4.16 ± 1.1	2.86 ± 0.8
	Lymphocytes	44.8 ± 1.70	41.9 ± 0.96	41.7 ± 4.8	42.4 ± 5.57

Leucocytes were purified from heparinized blood from two healthy volunteers and treated (or mock-treated) with increasing concentrations of bovine rIFN-λ (4.5; 9; and 18 IU/ml). After ON incubation, cells were stained with LIVE/DEAD^{TM} *Fixable Dead Cell Stain Kit and analyzed by FACS.* ***(A)*** *Lymphocytes were gated based on the morphological criteria (SSC vs. FSC cytogram), and the percentage of dead cells after each treatment was estimated.* ***(B)*** *Lymphocytes, monocytes, and granulocytes were gated based on the morphological criteria (SSC vs. FSC cytogram), and the percentage of total cells within each cell type was estimated and compared between treatments. Mean values ± SD from triplicate samples are depicted for each treatment.*

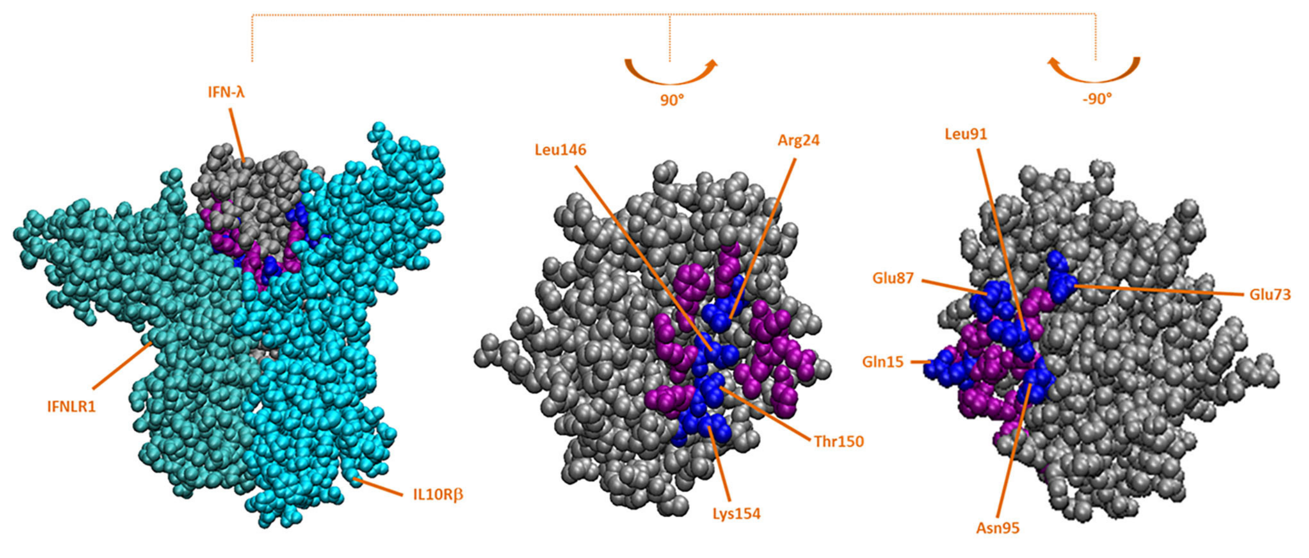

FIGURE 1 | Crystallographic structure of hIFN-λ and hIFN-λ/IFNLR *in silico*-mutated complex. Based on the crystallographic structure of the hIFN-λ3/IFNLR complex (PDB: 5T5W), IFN-λ residues in the interface with IFNLR were replaced with those present in the bovine interface using FoldX software. All residues in the IFN-λ interface are colored purple and blue, and mutated residues (in blue) are indicated. Left: mutated structure of the hIFN-λ/IFNLR1/IL10Rβ complex; side faces of mutated hIFN-λ interacting with IFNLR1 (center) and IL10Rβ (right).

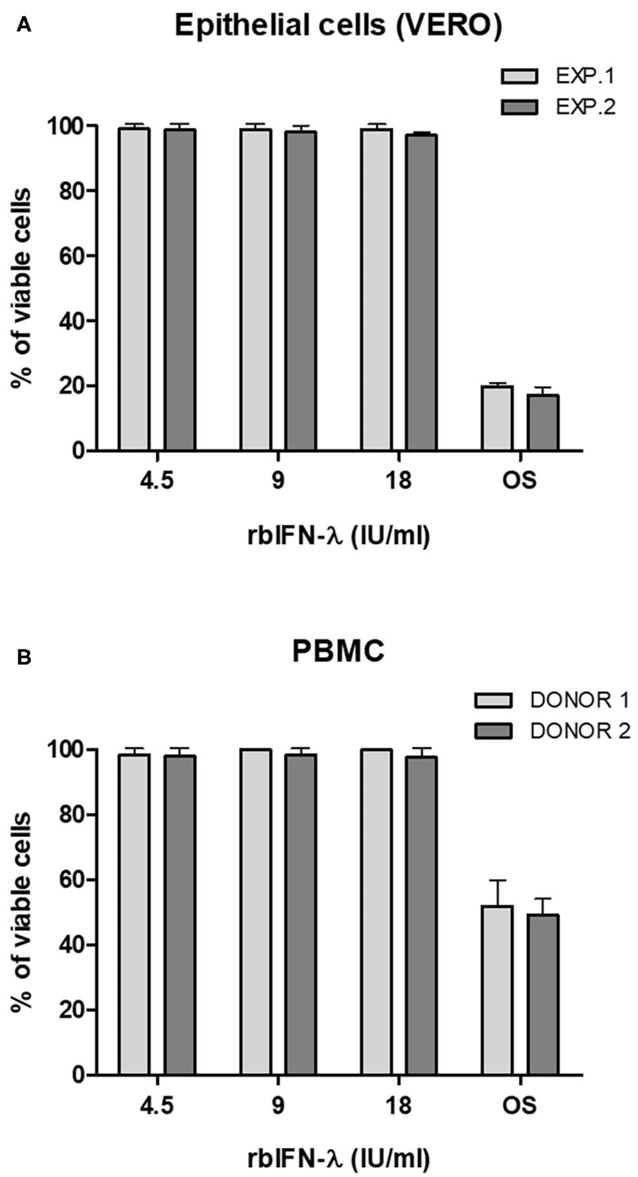

FIGURE 2 | Effect of the bovine rIFN-λ on the viability of VERO cells and human PBMCs. VERO cells **(A)** and PBMCs **(B)** were treated with 4.5, 9, and 18 IU/ml of recombinant bovine IFN-λ (rbIFN-λ) for 18 h and their capacity to reduce XTT was assessed. Control cell samples were also incubated ON with PBS to induce an osmotic shock (OS). Percentage of living cells was referred to values of mock-treated controls. Mean values ± SD from triplicate samples are depicted for each dilution for each experiment (EXP.) or human donor.

were used, and not different to those found in the mock-treated cells (**Table 3A**). Likewise, no changes in cell size or granularity were found after rbIFN-λ treatment, and the percentage of granulocytes, monocytes, and lymphocytes were almost identical between mock and rbIFN-λ treatments (**Table 3B**).

Safety of rbIFN-λ was then assessed by measuring the metabolic activity of VERO cells (**Figure 2A**) and human PBMCs (**Figure 2B**) after an ON incubation with the same concentrations

TABLE 4 | Effect of the bovine rIFN-λ on the induction of inflammatory responses in human immune cells.

		Treatment			
		Mock	**LPS**	**rbIFN-λ**	**LPS + rbIFN-λ**
Donor 1	IL-6	<2	>10,000	1,650	>10,000
	IL-10	<5	>1,000	22.2	391
Donor 2	IL-6	<2	>10,000	270	>10,000
	IL-10	<5	757	<5	117

Whole blood samples were stimulated ON with LPS (20 ng/ml), rbIFN-λ (18 IU/ml), a combination of both, or mock-treated with dilution buffer (PBS). IL-6 and IL-10 were quantified by a chemiluminescent assay, and values were expressed in pg/ml.

of rbIFN-λ used in the previous experiment. A colorimetric assay was used, and the percentage of living cells was referred to values of mock-treated cells. No changes in the viability of any of these cells were observed even at the highest rbIFN-λ concentration assayed.

Whole blood samples from the same donors were also treated ON with 18 IU/ml of rbIFN-λ, 20 ng/ml of LPS, and a mixture of rbIFN-λ and LPS. The following day, IL-6 and IL-10 levels were measured in stimulated plasma. Both IL-6 and IL-10 levels were lower in rbIFN-λ-treated PBMCs compared to LPS-treated samples. Interestingly, detection of IL-10 was reduced when LPS and rbIFN-λ were used together, compared to LPS alone (**Table 4**).

Activity of rbIFN-λ Against SARS-CoV-2

Activity of rbIFN-λ against SARS-CoV-2 was assessed in three independent experiments using samples run in quadruplicates. VERO cells were incubated ON with rbIFN-λ, human rIFN-α, or rIFN-β and infected with an Argentinean isolate of SARS-CoV-2. Mock-infected cells and IFN-treated non-infected wells were used as controls. Cultures were examined for CPE at 24 h and 48 h, when supernatants were recovered for quantitation of SARS-CoV-2 genome copies, and cells were fixed and stained for colorimetric assessment.

Incubation with rbIFN-λ did not produce any adverse effect in VERO cells even at the highest concentration (18 IU/ml). On the contrary, incubation with high concentrations of human rIFN-α and rIFN-β was toxic for the cells in culture. About 60% of the cells were killed by rhIFN-α and 25% were killed by rhIFN-β used at a concentration of 9 IU/ml (**Figures 3B,C**).

As shown in **Figure 3A**, the rbIFN-λ had a strong antiviral activity against SARS-CoV-2. The estimation of rbIFN-λ IC_{50} with the colorimetric assay was 0.045 IU/ml, 53 times lower than that of human IFN-α and almost 33 times lower than rhIFN-β. These results were consistent with CPE observation (**Figure 3** and **Supplementary File 3**).

RT-qPCR results also showed that all the concentrations of the rbIFN-λ tested caused a reduction of viral RNA copy number that was significant with respect to untreated infected cells ($p < 0.01$; **Figure 4**). Moreover, viral genome copy numbers were drastically reduced by 2 $\log_{10}$ units of magnitude at a concentration of 0.1 IU/ml and were almost undetectable by the assay at higher

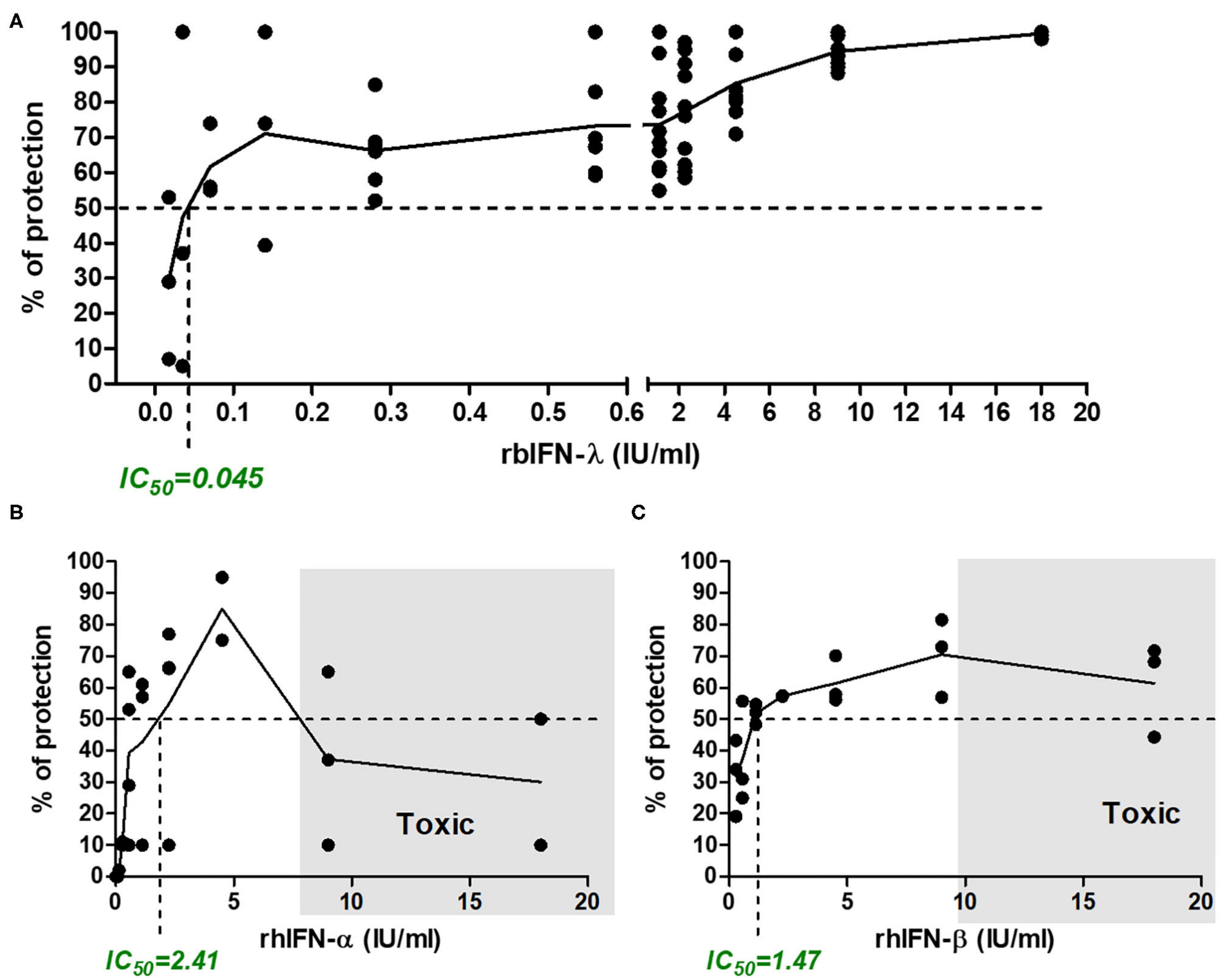

FIGURE 3 | Antiviral activity of bovine rIFN-λ in VERO cells infected with SARS-CoV-2. VERO cells were treated with serial dilutions of bovine rIFN-λ **(A)**, human rIFN-α **(B)**, or human rIFN-β **(C)**. After an ON incubation, cells were infected with SARS-CoV-2 (MOI = 0.5) and incubated for 48 h, when cytopathic effect was detected in untreated cells. Antiviral activity was estimated by staining the cell monolayers with crystal violet and reading the resulting OD at 575 nm. Percentage of protection was referred to values of mock-treated and infected cells. Toxicity controls were run in parallel in every experiment on treated uninfected cells. The inhibitory concentration 50% (IC_{50}, concentration required to inhibit SARS-CoV-2 infection in 50% of the replicates analyzed) is indicated in each chart. Shaded areas depict the toxic concentration range, defined as the concentration of IFN that induces a loss of viability in uninfected cells (a cytopathic-like effect is observed microscopically in IFN-treated but not infected wells, with an increasing number of dead cells, which is related to the low-OD 575-nm values).

concentrations of rbIFN-λ (**Figure 4A**). The incubation with rbIFN-λ at concentrations as low as 0.02 IU/ml reduced the yield of viral RNA produced by mock-treated infected cells to $<$ 10% (**Figure 4B**). We estimated that 0.008 IU/ml of rbIFN-λ might reduce the copy number of genomic viral RNA produced by untreated infected cells by 50%. These results demonstrate that rbIFN-λ is a potent inhibitor of the SARS-CoV-2 clinical Argentinean isolate.

DISCUSSION

Administration of IFNs can be used for prophylaxis and early therapy of COVID-19 compensating the weak IFN response in the first stages of human SARS-CoV-2 infection (38, 39). IFN-λ has several advantages compared to type-I IFNs and is already under clinical trials (40). In this study, we assessed the efficacy of a recombinant bovine IFN-λ against SARS-CoV-2. We confirmed the *in vitro* safety and enhanced efficacy of this IFN preventing SARS-CoV-2 infection in VERO cells at concentrations significantly lower than those required for recombinant human IFN-α and -β. To the best of our knowledge, this is the first time a bovine IFN has been proposed as a human biotherapeutic.

The use of bovine IFN-λ for human use is supported by its capability of activating the human Mx promoter (28); its high similarity with human IFN-λ1, 2, and 3; and a predicted higher affinity for the human IFNLR1/IL10Rβ heterodimeric receptor, at least in terms of free energy and dissociation

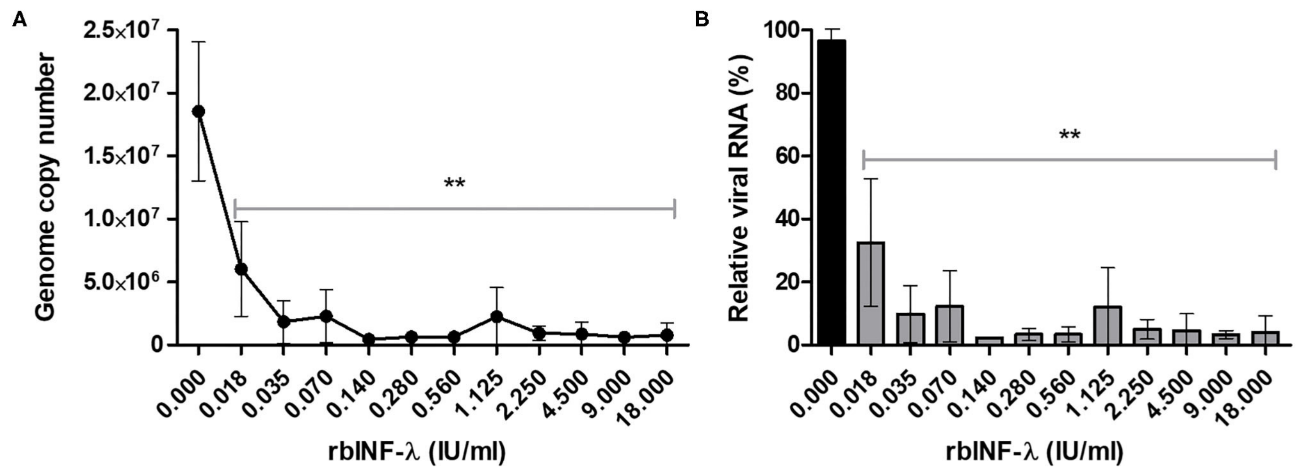

FIGURE 4 | Detection of SARS-CoV-2 genome. VERO cells were infected with serial dilutions of bovine rIFN-λ and SARS-CoV-2 RNA from culture supernatant samples and were quantified by qRT-PCR. Results are expressed as viral RNA copy number per milliliter **(A)** and percentage of relative viral RNA from mock-treated and infected cells **(B)**. Mean values ± SD from quadruplicate samples are depicted for each rbIFN-λ dilution. **Values significantly lower than those measured in the mock-treated and infected cells ($p < 0.01$).

constant. It is important to consider that due to the limited available crystallized structures, we modeled the rbIFN-λ using the human IFN-λ/IFNLR complex as template. Even though there are high similarities in the linear amino acid alignment, the predictive modeling is limited by the backbone conformation of the template and adjustments of side-chain stereochemistry-based differences with the model, possibly concealing real structural differences between the human and bovine proteins. Notwithstanding these limitations, our *in silico* analysis revealed that the enhanced affinity was mainly related to discrete amino acid substitutions. Interestingly, some of these positions had been mutagenized before to obtain a stable interaction for the crystallographic structure assessment (25). These observations support the idea that affinity of human IFN-λ for its receptor may be improved and that a heterologous IFN-λ (such as this rbIFN-λ) could have a better affinity for the human IFNLR. Improving IFN-λ affinity might increase the downstream signaling and improve the activation of the ISGs, reducing the effective dose needed for therapeutic use.

Safety of the rbIFN-λ in human immune cells was confirmed by using different viability assays. An ON incubation of rbIFN-λ in doses as high as 18 IU/ml with human PBMCs did not affect metabolic activity, viability, size, or granularity of these cells. No cytotoxicity signs were found for VERO cells even at higher concentrations than those that killed these cells when treated with recombinant human IFN-α and -β.

The rbIFN-λ induced a cytokine pattern on human PBMCs similar to that reported for human IFN-λ, upregulating IL-6 and inducing low levels of IL-10 (41), thus confirming a comparable immune activity of rbIFN-λ in human immune cells. This cytokine profile is expected to activate the innate immunity at the site of viral infection and promote the development of the acquired immunity. Our results show that the co-treatment of PBMCs with rbIFN-λ and LPS reduced IL-10 levels compared to LPS alone, which can modulate inflammation produced by bacterial infections (42, 43). The limited proinflammatory effect is one of the most relevant advantages of IFN-λ compared to type 1 IFNs (44), particularly for treating COVID-19, as inflammation has been associated with the development of severe disease. However, the direct effect of IFN-λ on COVID-19 progression remains unclear and the responsiveness of human immune cells to IFN-λ is still being analyzed (22). In this scenario and with IFN-λ being quite recently discovered (45, 46), more work is needed to elucidate the role of this cytokine and the timing of its application to prevent or reduce the progression of COVID-19.

Several studies show that type I and type III IFNs are effective in reducing SARS-CoV-2 replication in VERO cells (18, 19, 47).

Lokugamage et al. recently demonstrated that a pretreatment of VERO cells with 1,000 IU/ml of human IFN-α caused a 2-$\log_{10}$ drop in viral titer at 48 dpi as compared to control untreated cells (47). We found the same result but using 0.14 IU/ml of rbIFN-λ. Another study from Mantlo et al. (19) estimated the IC_{50} of IFN-α and IFN-β treatment of VERO cells before SARS-CoV-2 infection to be 1.35 IU/ml and 0.76 IU/ml, respectively. These values are similar to those estimated here for type I human IFNs and over 30 times higher than the one computed in this study for the rbIFN-λ. Although comparisons are difficult due to the use of different IFN-quantitation methods and the various readouts used for the infection assessments, bovine IFN-λ seems to be more efficient than human type I IFNs to prevent SARS-CoV-2 infection *in vitro*.

Felgenhauer et al. showed that 10 ng/ml of rhIFN-λ significantly reduced SARS-CoV-2 titers in VERO cells. Using our production method, we estimate that 1 IU corresponds to 10 ng of rbIFN-λ, meaning that 0.17 ng of our rbIFN-λ (0.0175 IU/ml) would be sufficient to reducing SARS-CoV-2 replication in VERO cells. These results suggest that about 50 times lower concentrations of bovine IFN-λ are required to achieve a similar reduction rate than that achieved by human IFN-λ (18). These estimations will be confirmed by a side-by-side assay using recombinant human IFN-λ in future experiments.

Our results demonstrate that rbIFN-λ is more efficient than two recombinant human type I (α- and β-) IFNs in impeding SARS-CoV-2 infection in VERO cells. This evidence, together with its low *in vitro* toxicity, the biological functions of the type III IFNs, its high-sequence identity with human counterparts, and its predicted enhanced binding capacity to the human IFNLR, supports further evaluations of the rbIFN-λ as a potential biotherapeutic compound for COVID-19 that could be produced at affordable costs. Moreover, this strategy could be tested against other respiratory viral infections that may emerge.

We have already proved the versatility of producing active rbIFN-λ in HEK-293 cells, *Escherichia coli*, or by using a recombinant baculovirus in insect cells (data not shown). We envision a formulation that can be administered locally through an inhaler (puffer) or using a nebulizer either early after infection or as a preventive measure, two options that have been successfully applied for human IFNs (39). A simple administration method and the expected low cost of this antiviral are paramount issues for low–middle-income countries (LMIC) like ours, with significant percentages of the population with limited access to health services and lacking even basic healthcare needs. These therapeutic alternatives may also be relevant in a middle-term scenario for LMIC where COVID-19 vaccines will be available on limited grounds and firstly used in the high-risk population, reinforcing the need for a low-cost therapeutic to counteract future waves of SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the committee approved the use of human blood samples for our *in vitro* experiments. Our protocol was approved by the Comité de Ética Central of the Buenos Aires Province Government, Exp 2919-2182-2020, resolution number ACTA-2020-16644926-GDEBA-CECMSALGP dated August 12th, 2020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NC and FM developed the IFN-λ batch, carried out most of the experiments, and helped in data analyses. EBe did all the experiments with live virus supervised by EBa. LB and JI carried out all the bioinformatics evaluations. IS performed the flow cytometry analyses. CT and LB analyzed all relevant literature and helped in drafting the manuscript. AC designed and directed the study, analyzed the data, and wrote the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.603622/full#supplementary-material

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The COVID-19 Pandemic and Global Food Security

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We present scientific perspectives on the impact of the COVID-19 pandemic and global food security. International organizations and current evidence based on other respiratory viruses suggests COVID-19 is not a food safety issue, i.e., there is no evidence associating food or food packaging with the transmission of the virus causing COVID-19 (SARS-CoV-2), yet an abundance of precaution for this exposure route seems appropriate. The pandemic, however, has had a dramatic impact on the food system, with direct and indirect consequences on lives and livelihoods of people, plants, and animals. Given the complexity of the system at risk, it is likely that some of these consequences are still to emerge over time. To date, the direct and indirect consequences of the pandemic have been substantial including restrictions on agricultural workers, planting, current and future harvests; shifts in agricultural livelihoods and food availability; food safety; plant and animal health and animal welfare; human nutrition and health; along with changes in public policies. All aspects are crucial to food security that would require "One Health" approaches as the concept may be able to manage risks in a cost-effective way with cross-sectoral, coordinated investments in human, environmental, and animal health. Like climate change, the effects of the COVID-19 pandemic will be most acutely felt by the poorest and most vulnerable countries and communities. Ultimately, to prepare for future outbreaks or threats to food systems, we must take into account the Sustainable Development Goals of the United Nations and a "Planetary Health" perspective.

Keywords: COVID-19, food security, One Health, Planetary Health, SARS-CoV-2, food safety, animal production

INTRODUCTION

Food security is central to the United Nations 2030 Agenda for Sustainable Development Goals (SDG), which aim to end poverty and protect the planet from environmental degradation (1). Framed around these SDGs, the concept of "Planetary Health" emphasizes the understanding that human health and human civilization depend on wealthy natural systems and their prudent stewardship (2, 3). In addition to existing environmental changes (e.g., droughts, floods, extensive wildfires, typhoons, sea-level rise, etc.) that have recently led to major food crises (4), the world is now experiencing the worst pandemic since the Spanish flu in 1918.

SARS-CoV-2 is the causative agent of COVID-19, a zoonotic respiratory epidemic that has been declared by the World Health Organization (WHO) as a global public health emergency (5). At the time of this writing, almost 10 months after the first case was discovered, the SARS-CoV-2 virus has affected more than 30 million people in 188 countries, and caused more than 1 million deaths (6). Both the disease and the fear of disease have triggered substantial global economic and social impacts, along with restrictions on international travel imposed by most countries, the quarantining of millions of people, dramatic declines in the tourism and hospitality industries, and disruption of supply chains for food, medicines, and manufactured products (7). As noted by food safety authorities, there is no evidence as yet associating the consumption of contaminated food or contaminated food packaging as routes of transmission of SARS-CoV-2 (8), yet taking precautions for this exposure route seems necessary.

The Food and Agriculture Organization of the United Nations (18) states that COVID-19 affects agriculture in two relevant aspects: the supply and demand for food. These two aspects place food security at risk in many key aspects of the food system value chain. We present examples where COVID-19 can impact food security in the short-, medium- and long-term based, primarily, on literature searches conducted independently by all authors. Searches were retrieved from electronic databases including Web of Science and Pubmed through the use of multiple keyworks and expressions, for example, (COVID* OR coronavirus OR Sars-CoV-2) AND (food OR safety OR security OR nutrition) AND (nutrition* OR health* OR policy OR policies) that were collected in a reference manager system. In addition, gray literature including reports from international organizations, governments and non-governmental organizations and news from media were included upon agreement from all authors. Searches were restricted to include publications from 1 January through 1 September 2020.

We also provide sustainable "One Health" pathways to action which address the multi-dimensional nature of zoonotic and food-borne disease challenges, and which move preparedness and contingency planning for future threats to the food systems. "One Health" is a concept "*to address a health threat at the human-animal-environment interface based on collaboration, communication, and coordination across all relevant sectors and disciplines, with the ultimate goal of achieving optimal health outcomes for both people and animals; a 'One Health' approach is applicable at the subnational, national, regional, and global level*" (9). Ultimately, COVID-19 provides an opportunity to move toward a holistic "Planetary Health" approach, defined as "*the health of human civilization and the state of the natural systems on which it depends*" (2, 3).

IMPACTS ON AGRICULTURAL LIVELIHOODS AND FOOD AVAILABILITY

COVID-19 has disrupted many activities in fisheries, livestock, agriculture, and their supply chains; with outbreaks that have closed numerous facilities worldwide (10, 11). The use of quarantines, bans, restrictions on the movement of goods and people as disease control measures has resulted in significant socio-economic repercussions for livelihoods especially for poor rural farmers, livestock keepers, and capture fisheries from developing nations (7). Estimates on the economic fallout brought by the COVID-19 pandemic indicate that over half a billion people may be pushed into poverty. Of these, communities in Sub-Saharan Africa, North Africa and the Middle East are expected to be the hardest hit (12). Particularly, central and Southern Asia and sub-Saharan Africa, home to 87% of the world's extreme poor, will see the largest increases in extreme poverty, with an additional 54 million and 24 million people, respectively, living below the international poverty line as a result of the pandemic (13). Small island development states (SIDS) that depend on food imports will also be impacted.[1] These sanitary restrictions, often indispensable to reduce the spread of the virus, also cause the frequent disruption of both market chains and trade of agricultural and non-agricultural products, entailing major potential impacts on the segments of the population that rely on them to sustain their livelihoods and their food and nutrition security (14).

Movement restrictions have reduced the availability of migrant labor, interrupting some harvesting and agricultural activities, increasing levels of post-harvest losses due to reduced workforce, and delaying the delivery of fresh produce to various target markets (15). Some examples include affected coffee growers in Brazil and Colombia, mango producers in Pakistan, and livestock in the UK. Although primary production may not appear to have suffered as harshly, a particular challenge in the short term will be to provide access to food for those in the population that are taking strict sanitary measures, particularly those who have lost their jobs and/or those in urban areas in countries where movement controls have limited the volumes of food traded from rural areas (16).

COVID-19 related disruptions and trends have made importers to continue facing insecurity in freight pricing, capacity, and demand volume across many modes of transport.[2] These restrictions may also impact agricultural input markets by increasing the costs of storage at port and reducing the availability of seeds and fertilizer.[3] There may also be a negative effect on animal feed and the ingredients necessary for the preparation of food, in particular those dependent on imports for their availability. China and India are countries of origin for many primary ingredients for both food and non-food imports, such as active pharmaceutical ingredients (17). Reliance on small numbers of overseas markets and channels of distribution, offers little resilience in the face of disruptions caused by this pandemic. The FAO has recommended facilitating transport and economic access to productive inputs (seeds, fertilizers, feed, etc.), along with access to machinery and infrastructure to ensure food supplies (18). Agriculture Ministers from the

[1]https://www.theguardian.com/world/2020/jul/11/job-killer-of-the-century-economies-of-pacific-islands-face-collapse-over-covid-19

[2]https://www.freightos.com/freight-resources/coronavirus-updates/

[3]https://ihsmarkit.com/research-analysis/report-covid19-effects-on-the-fertilizer-industry.html

G20, African Union, ASEAN countries and Latin America and Caribbean (LAC) have agreed to keep global food markets open and refrain from imposing new trade barriers to ensure food flows between countries.

Informal, low-paid, and migrant workers are already highly vulnerable to food insecurity, defined as "*unreliable physical, social, and economic access to sources of adequate and nutritious food that meets people's dietary needs and food preferences*" (19). As a result of COVID-19, many have lost their jobs (20) and received no state support, with no social protection nets to allay potential impacts on hunger. Women largely work in the informal sector and face significant income losses as well.[4] This is of particular relevance in conflict-affected places which host their displaced populations (21, 22).

Other workers continue their activities in conditions rife with poverty and in overcrowded spaces, which greatly increases the risk of contracting the disease. Informal markets have been closed down in several African countries, even though these markets are essential to provide vital food and sales outlets for low income consumers and low-income farmers and traders respectively. In such places, night markets, farmers' markets and roadside stalls are not allowed to operate during the movement control order, and many vegetable truck drivers have stopped their services as well, due to restrictions on traffic and operating hours, which has affected the food production chain (23).

While FAO (18) has noted that LAC and international traders have enough stocks to feed their populations in the next months, looking toward the longer-term, challenges to international trade, farm financial stability, and transportation remain in place (24). To maintain the availability of basic foods, it is key to maintain the operation of agricultural farms, with special attention to small scale farmers, but without excluding larger ones. Supporting the transportation, processing and packaging of agricultural and fishery products, solving logistical problems of food value chains and guaranteeing the operation of retail outlets, markets and supermarkets are key measures to keep the regional food system alive.

IMPACTS ON FOOD SAFETY

The risk of COVID-19 exposure and transmission via contact with domestic food-producing animals such as chickens, ducks, other poultry, pigs, cattle, horses or sheep or through consumption of contaminated food or exposure to food packages is currently considered negligible (25). However, concerns have been raised about the risks of human exposure to COVID-19 through the consumption of aquatic animals, such as finfish, crustaceans, mollusks and amphibians (26). Beijing has recently recorded dozens of new cases, all linked to a major wholesale fresh food market, raising concerns about a resurgence of the disease through this route of transmission.

The SARS-CoV-2 virus cannot multiply in food and requires an animal or human host to multiply. Aerosol and fomite transmission of the virus is the primary route of transmission and the virus can remain viable and infectious in aerosols for hours and survives on surfaces for days (27). There is not current scientific evidence to suggest that the virus is transmitted by eating contaminated food (28) nor can the virus grow or multiply on the surface of food stored in a cupboard, fridge, or freezer (29). However, it is possible that food animals and their products, as with other surfaces, could become contaminated with SARS-CoV-2 when handled by infected people that may shed the virus. New data have shown that SARS-CoV-2, in certain environmental conditions (e.g., 21–23°C), could survive in plastic for up to 3 days, in stainless steel for 2 days, and in cardboard for 1-day (27); this representing a potential risk and emphasize the importance of handwashing and good hygiene. While COVID-infected individuals have reported gastrointestinal symptoms with some having viral RNA or live virus in feces (30), viral RNA has also been detected in sewage (31, 32), suggesting that fecal-oral transmission is another possible route for exposure.

Guidelines to mitigate risks of COVID-19 have been provided by the World Health Organization (WHO),[5] the European Food Safety Authority (EFSA),[6] the Food and Drug Administration (FDA),[7] and the German Federal Institute for Risk Assessment (BfR).[8] In addition, industry and relevant food business operators have taken important steps toward the reinforcement of measures for personal hygiene and food hygiene principles, in the form of refresher training, so as to help food workers reduce or eliminate the risk of contamination with the virus on food surfaces and food packaging materials. Nevertheless, the food industry has still been affected by facility closures (33) and numerous outbreaks (34). Data from the US indicates that there have been at least 32,000 COVID-19 cases related to employees of food systems, and most of these cases (∼84%) have occurred in workers of meatpacking facilities (**Figure 1**). While not human COVID-19 cases have been attributed to the consumption or handling of raw meat or either food products from closed facilities were not recalled by FDA (35); environmental conditions of temperature and moisture at meat plants may facilitate SARS-CoV-2 indoor dispersal (36).

Meat processing plants, the meat packing industry and the poultry processing industry have been involved in superspreading events of COVID-19, particularly in the US, where, for example, the Smithfield plant in South Dakota accounts for 44% of all diagnoses in the state, making the largest single-source hot spot for the virus nationwide. In Minnesota, plant shutdowns have forced hog farmers to kill and dispose with the bodies of over 300,000 pigs. The ability to manage plant shutdowns downstream rests on the upstream capacity of the farm to manage more and larger animals, understood as providing enough space to house, feed and water them. Ideally,

[4] https://blogs.worldbank.org/developmenttalk/covid-19-pivotal-moment-support-women-farmers

[5] https://www.who.int/publications/i/item/covid-19-and-food-safety-guidance-for-food-businesses

[6] https://www.efsa.europa.eu/en/news/coronavirus-no-evidence-food-source-or-transmission-route

[7] https://www.fda.gov/food/food-safety-during-emergencies/food-safety-and-coronavirus-disease-2019-covid-19

[8] https://www.bfr.bund.de/cm/349/can-the-new-type-of-coronavirus-be-transmitted-via-food-and-objects.pdf

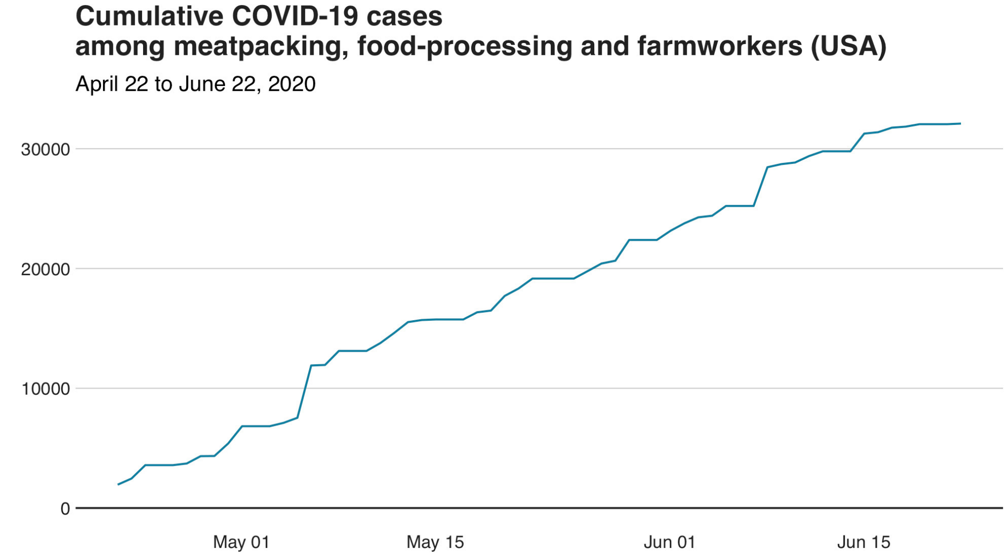

FIGURE 1 | Cumulative number of total COVID-19 cases among meatpacking, food-processing and farmworkers in the US from April 22nd to June 22nd, 2020 (Source: Food and Environment Reporting Network at www.thefern.org).

animals would be sent to a different abattoir to be processed, but this option is not necessarily available in every country, due to factors such as the lack of adequate means of transportation; unsuitable conditions of the alternate plant for the handling of a species or a certain animal size (e.g., incompatible equipment); not enough capacity for the accommodation of more animals; or a lack of personnel not unlike that affecting the original facility. Close to two million chickens had to be disposed of in Delaware due to a 50% shortage of personnel produced by the pandemic. In other words, there were simply not enough workers to process them, and there was insufficient space at their facility.

Reports of COVID-19 affecting food systems through contaminated imports has had negative consequences for industry, despite limited evidence of spread through this pathway. For example, China suspended imports from a pork plant in Germany and a chicken processor in the US, when a COVID-19 outbreak occurred (37, 38), while a beef unit in Brazil and a British pork plant voluntarily stopped exports to China after workers tested positive (39). While none of the outbreaks have been attributed to eating or handling contaminated food; in terms of current data, a recent pre-print showed that the titer of SARS-CoV-2 in artificially contaminated pieces of salmon, chicken and pork with 3×10^6 $TCDI_{50}$ (median tissue culture infectious dose) was stable at 4, −20°C, and −80°C (40). This is indicating that for some countries that appears to have eradicated the virus, there is a potential fear of re-emergence of COVID-19 by contaminated food and food packaging.

For decades, food producers have implemented food safety plans as pre-requisite programs, which include good hygienic practices. Despite this, there is still a lack of experience and evidence available on the risks of exposure and onward transmission of COVID-19 via food production workers. Risk assessments and implementation of effective interventions such as face masks and shields have been implemented to refine Food Safety Programs.[9] More importantly, maintaining the safety and quality of food is critical, including the maintenance of testing for other known foodborne pathogens (e.g., *Listeria monocytogenes* and *Salmonella*), which could worsen the crisis in case of an outbreak (41). Countries and food industries should provide guidelines to stress any additional measures to ensure that the food chain is maintained, providing adequate and safe food supplies for consumers.

IMPACTS ON PLANT AND ANIMAL HEALTH AND ANIMAL WELFARE

COVID-19 has compounded the impacts of other emerging and existing animal and plant disease threats, worsening health outcomes across different sectors and disproportionately affecting already marginalized populations (10, 11). For example, the regional and temporal clustering of COVID-19 outbreaks alongside climate change impacts (including severe weather such as flooding, droughts, heat waves, desertification, etc.), has exacerbated negative effects associated with the concurrent spread of other pests such as the desert locust plague (10, 11, 42). COVID-19 has reduced peoples' ability to conduct locust surveillance and control programs; the locusts have decimated food crops and forage in East Africa, India and Pakistan and this, in combination with severe economic crises in these countries, suggests that the negative health impacts of food insecurity may be felt long after the pandemic is over. Another example is the spread of the African Swine Fever virus (ASFv) in Asia (43). ASF does not pose any risk to human health but is a highly

[9]https://instituteforfoodsafety.cornell.edu/coronavirus-covid-19/background-info-covid-19/peer-reviewed-papers/

contagious (and fatal) viral disease of domestic and wild pigs. ASFv is responsible for serious production and economic losses and in 2019 reduced pig stocks in Southeast and East Asia, particularly China and Vietnam. Outbreaks remain ongoing in the region. Fighting and controlling pests and epidemics during a global pandemic is a potentially catastrophic combination that demands urgent responses in many countries, but also binds policymakers into making critical tradeoffs with the deployment of resources to address multi-faceted shocks. Thus, planning and preparation for epidemic prevention and control are essential.

IMPACTS ON HUMAN NUTRITION AND HEALTH

According to the estimates provided by the Global Report on Food Crises, in 2019, 135 million people were food insecure. More recent projections from the World Food Programme, however, indicate that this number may double to 265 million people in 2020, as a consequence of the effects the pandemic on the economy and the disruptions it has caused in supply chains (44). The pandemic brought by COVID-19 has put into display how the food, health and socioeconomic systems determining food outcomes are intricately interconnected. It has exposed again, how these systems currently operate in a manner that shields the richest and most powerful from many of the hardships of the pandemic (45).

The COVID-19 pandemic is creating worrying impacts on household incomes, food supply chains, health services, and schools (46). Moreover, strategies such as social distancing and hygiene measures like frequent handwashing are difficult to put into practice for the millions of people living in high density communities and whose housing is either precarious or insecure, with poor sanitation conditions and limited access to clean water. Many of those affected also face malnutrition and suffer from non-communicable diseases, and infectious diseases such as HIV/AIDS and tuberculosis (47). When the crisis began, an estimated 10.5 million children under the age of five suffered from wasting, 78 million children presented stunted growth, and 17 million were overweight, together with some 400 million women suffering from anemia (35). The present circumstances only worsen the difficulties already faced by a great number of families to access affordable and healthy diets.

The COVID-19 pandemic is causing an enormous impact on the nutrition status of the poorest and most vulnerable members of the population, and this impact should be regarded as a major concern. As demonstrated by the ecology of adversity and resilience, the health effects of substantial stressors, including inadequate nutrition, can lead to long-term effects (48). Indeed, poor-quality diets are linked to physical and also mental health (49). Recently, a recommended framework to sustain optimal nutrition from individual to global levels has been proposed to alleviate the impact of COVID-19 on nutrition and food security (50). FAO has also provided a set of guidelines on food systems and nutrition aimed at contributing to transform food systems and to promote sustainable food systems.[10] Abundant literature exists on the relationship between food insecurity and poor health outcomes in children. Food insecurity has effects not only on human health but also on mental health. There is a higher risk of depression as well as suicidal ideation in adolescents, while chronic conditions, such as asthma, become more frequent. Iron deficiency, among other nutrient deficiencies, are known to be associated to impaired learning and decreased productivity in schoolchildren (51). Further evidence is required to understand the short and longer-term impact of COVID-19 on dietary intakes and resultant human nutrition and health. Low access to animal source foods, fruits, and vegetables has long term consequences, through poor child physical and cognitive development (52).

POLICIES TO ADDRESS FOOD SECURITY: CURRENT AND FUTURE APPROACHES

The post-pandemic phase may result in key changes within the food systems with emphasis on strengthening resilience to address the inequality of accessing healthy food (4). For example, locally produced food may be an opportunity for a new agri-food system that would reduce long-distance transportation and distribution by third parties with significant carbon footprints, although the evidence is mixed as to whether local production is always more "climate-friendly" (53). As in other conflicts, uncertainties about and/or an absence of governance, weakened institutions, changing donor funding priorities/involvement and diminished local research capacity constrain traditional opportunities for long-term contingency planning and access to and integration of local expertise that is essential for timely, evidence-based decision-making (54). Previous global outbreaks like Ebola (55) had adverse impacts on food and nutrition security, mostly for vulnerable populations including children and elderly, women, and the poor.

New or adapted policies will need to address tax and trade rules to continue the supply chain and adopting fiscal measures in case food prices abruptly increase (18). Currently, cash and in-kind transfers, new credit lines for strategic actors in the food chain, subsidies, loans and income support for families, distribution programs (e.g., food banks), and continuing school-feeding delivery for the most vulnerable and poorest people have been implemented to maintain trade and food supply chains while promoting social protection to ensure food access (56). Prices have declined for raw commodities such as wheat, vegetables, and other crops, yet consumers are often paying more for processed food products.

Last March, the United Nations allocated US$2 billion for a COVID-19 Global Humanitarian Response Plan, intended for agencies such as WHO, UNICEF, and the WFP to reach out to the most vulnerable communities and provide them with food, water and sanitation, and vaccinations, as well as testing materials COVID-19 and medical equipment (57).

[10]http://www.fao.org/cfs/workingspace/workstreams/nutrition-workstream/e

Recommended Actions

- **Accelerate progress toward the Sustainable Development Goals and strengthen local and global food systems by supporting local production, rural small-scale producer communities and backyard gardens in low middle-income countries**. Small scale farmers in Africa produce 72% of livestock derived foods (58). Such support will promote families and communities to feed themselves with diverse food and supporting the nearby urban areas with regular supplies. This approach has been proposed for Africa (59), where a strategic focus is required to provide key grassroot players in the food system, such as the communities of producers, fishers, pastoralists, indigenous peoples and others, with all the support and facilities they need.
- **Engage with consumers as well as producers to improve food system resilience to shocks.** Food systems are considered to be an important driver of climate change (60), with emergent impacts on the prevalence and distribution of novel infectious zoonotic and animal diseases as well as other direct impacts on greenhouse gas emissions and biodiversity loss (61). Understanding and influencing patterns of household consumption may play a powerful role in addressing resultant environmental and social impacts, as well as acting as a driver of reduced economic activity (62).
- **Identify unintended consequences and trade-offs of cross-sectoral interventions and policies to "future-proof" food systems.** For example, rewilding policies which aim to repair damaged ecosystems and restore degraded landscapes (63) may have indirect and unforeseen effects on human health and welfare including increases in traffic incidents and changes in disease dynamics (e.g., zoonosis) (64). Rampant deforestation, uncontrolled expansion and intensification of agriculture, and damaging activities such as drilling, mining, and infrastructure development are examples of unsustainable exploitation of wild nature and natural resources that have been recognized as main drivers for the incubation and transmission of diseases. Developing well designed rewilding plans demands a thorough understanding of interacting ecosystem processes and the socioeconomic context in which rewilding takes place.
- **Adopt risk-based approaches to target future interventions and policies to mitigate future shocks in the global food system and improve food security.** Despite the difficulty in predicting the impact of COVID-19, it is possible to determine the likely sources of transmission and forescast impacts on the most vulnerable. Risk-based approaches should focus on prevention strategies that are compatible with the local social context and a safe re-opening of the domestic economy with emphasis on food security. Relatively simple policies to encourage measures like the use of masks and handwashing stations to be put in place among informal markets would allow them to stay open and minimize risks to consumers and workers. More integrated approaches should use disease modeling or risk assessment frameworks as tools to support the decision-making process.
- **Increase/develop relevant research capacity and expertise through interdisciplinary training and research funding for scientists and practitioners**. Shocks to food systems, such as COVID-19 extend beyond a single-sector approach, demanding mobilization and integration of knowledge and skills across geographic, institutional and disciplinary boundaries. Sustainable food systems in the era of pandemics will require food production assistance and new tools, which include analyzing animal health and food safety through systematic approaches that will supply decision makers with significant added value (65).
- **Promote "One Health" and "Planetary Health" perspectives to cut across traditional domains to address the challenge posed by COVID-19.** The pandemic demonstrates our increasingly global, interdependent, and environmentally constrained societies. Broad integrated perspectives within the wider context of the SDGs are needed to properly address the impact of COVID-19, emerging infectious diseases and health threats on economics, international trade, politics, and inequality. In the future, our ability to prevent diseases and mitigate its impacts will depend on our competence to scale up action on the environment and avoid ruptures of ecological boundaries.

CONCLUSIONS

The global COVID-19 pandemic, along with the implemented social distancing efforts intended to slow down its spread (66), have brought economies and food systems into disruption at a global and local scale, with wide ranging ramifications in terms of food security. Food insecurity is likely to lead into serious consequences in terms of public health.

Public health, which is largely how the COVID-19 response has been led and initially classified, appears to be insufficient to describe or deal with the consequences of this type of pandemic. Moreover, COVID-19 highlights that the concept of "One Health" covers more than just the emergence of an infectious disease, but also extends to food-related health outcomes. Ultimately, to prepare for future outbreaks or threats to food systems, one must to take into account the SDGs and "Planetary Health." By doing so, we should be able to mitigate the impact of larger societal and political risks such as vulnerability, livelihoods, etc., and their interactions with the natural environment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

FM initially wrote the perspective and made **Figure 1** based on COVID-19 cases at meatpacking facilities in the US. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Impact of the COVID-19 Pandemic on the Welfare of Animals in Australia

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We report on the various responses in Australia during 2020 to minimize negative impacts of the COVID-19 pandemic on the welfare of animals. Most organizations and individuals with animals under their care had emergency preparedness plans in place for various scenarios; however, the restrictions on human movement to contain the spread of COVID-19, coupled with the economic impact and the health effects of COVID-19 on the skilled workforce, constituted a new threat to animal welfare for which there was no blueprint. The spontaneous formation of a national, multisectoral response group on animal welfare, consisting of more than 34 organizations with animals under their care, facilitated information flow during the crisis, which helped to mitigate some of the shocks to different organizations and to ensure continuity of care for animals during the pandemic. We conclude that animal welfare is a shared responsibility, and accordingly, a multisectoral approach to animal welfare during a crisis is required. Our experience demonstrates that to safeguard animal welfare during crises, nations should consider the following: a national risk assessment, clear communication channels, contingency plans for animal welfare, a crisis response group, and support systems for animal care providers. Our findings and recommendations from the Australian context may inform other countries to ensure that animal welfare is not compromised during the course of unpredictable events.

Keywords: animal welfare, COVID-19 pandemic, cross-sectoral collaboration, stakeholder networks, Australia

INTRODUCTION

In early 2020, humanity faced an almost unprecedented situation when a novel coronavirus named SARS-CoV-2, causing a disease known as COVID-19, changed life around the world (1). The virus continues to cause death, illness, strain on health systems, societal disruption, and economic damage. Based on experience with other pandemics, like the 1918 influenza pandemic, COVID-19 will likely disrupt human society for years to come (2). The World Health Organization (WHO) described SARS-CoV-2 as "a new strain [of coronavirus] that has not been previously identified in humans" (3). On 30 January 2020 the WHO declared the COVID-19 outbreak to be a "Public Health Emergency of International Concern" (4). On 28 February 2020 the WHO raised COVID-19 to the highest level of global risk (5). Many countries, including Australia, implemented measures that were aimed at reducing the spread of COVID-19, including restrictions on human movement, improved hygiene, and social distancing (henceforth referred to as physical distancing) to reduce human contact.

In Australia, the rapid introduction of government restrictions on human movement posed complex challenges, because Australia is a federation of states and territories (6). On 19 March 2020, the Australian Federal Government closed international borders to all non-citizens and non-residents (7) and then from 26 March 2020, state governments limited travel between all Australian states (8) and to remote communities (9). Meanwhile, on 16 March 2020, the Australian Federal Government imposed physical distancing, and state governments restricted the number of people who could gather in a group, from two to five people, depending on the state (10, 11). Consequently, many public places were closed, including cafes and restaurants, nightclubs, theaters, cinemas, concert halls, zoos, aquariums, and wildlife parks. The containment measures were effective in curtailing new infections, and in June, restrictions were gradually eased (12). A second wave of infections in the state of Victoria in late June prompted the Victorian Premier to place the Melbourne metropolitan area and the Mitchell Shire under tighter restrictions from 7 July 2020 (13). On 2 August 2020, restrictions were expanded to the remainder of the state, and Victoria entered a State of Disaster (14). In response, other jurisdictions tightened their restrictions on the entry of people coming from declared hot spots (15).

Both the health effects of COVID-19 and the measures to contain the pandemic created challenges for the economy, employment, food supply and consumption, and human social activities. Consequently, the pandemic threatened to impact the welfare of animals. Animals are integral to human society. Animals contribute to human well-being, and their welfare often depends on the capacity of humans to provide care for them. In Australia, animal welfare is regulated by legislation in each jurisdiction. The legislation promotes that organizations and individuals with animals under their care plan ahead for the welfare of the animals (16–24). Most organizations with a responsibility for animals have in place emergency preparedness plans for natural disasters and animal disease outbreaks. Nevertheless, these plans were not always suitable for coping with an unpredictable event, such as the COVID-19 pandemic.

A significant risk to animal welfare that defied planning was the extent to which human movement was restricted. The need to restrict human movement and limit social gatherings was identified at the Federal level as early as March, but the manner of implementation of "do not leave home" orders varied between jurisdictions and even local regions. Therefore, multiple organizations made requests to governments for explicit permission for movement associated with animal care (e.g., veterinary care and routine husbandry). Along these lines, the classification of veterinarians, livestock transporters, and animal welfare inspectors as essential services was also pursued by many organizations that are responsible for animal care. In response to these requests, movement restrictions were discussed in a meeting of officials from state, territory and Federal departments on 17 April, and the meeting of Ministers of Agriculture from all jurisdictions on 7 May. Subsequently, the issue of movement restrictions was resolved through clarifications by State and Territory Governments up to the start of the second wave in Victoria. Border restrictions with Victoria were tightened again, causing additional challenges for those moving animals and caring for animals across borders.

In addition to the governmental responses, other sectors of Australian society responded to the COVID-19 pandemic. In the remainder of this article, for each industry and organization that deals with animals and their welfare (hereafter referred to as sectors), we outline the specific effects of the COVID-19 pandemic on the sector and on the welfare of their animals. Where appropriate, we discuss their level of preparedness. Then we describe the spontaneous formation of a national, multisectoral response group, and how this group assisted different animal sectors in dealing with the impacts of the COVID-19 pandemic on animal welfare. We conclude with several recommendations that might be beneficial to countries and groups in safeguarding animal welfare in the course of unpredictable events.

SECTOR RESPONSES TO THE COVID-19 PANDEMIC

Red Meat Production

During the early stages of the COVID-19 pandemic there was concern that livestock transport across state and intrastate borders would be restricted and that supply chains would be disrupted, which could impact the welfare of animals in that chain. In Australia, livestock are often transported long distances across borders. In the early weeks of the containment measures, there was panic buying of red meat at supermarkets (25), which put pressure on the supply chain and the demand for transport. There was also concern that livestock saleyards would close because their operation requires the gathering of people. Several organizations that represent the red meat sector sought clarification from authorities, and urged authorities to classify movements that are associated with livestock production as essential services (26). An industry response was coordinated by several peak industry bodies. There were guidelines released around physical distancing in saleyards, and online bidding was encouraged as an alternative to physically attending sales (27). The Australian Federal Government also provided visa extensions for agricultural workers to ensure ongoing support for the husbandry requirements of livestock production (28). Furthermore, in March 2020 the Australian Federal Government introduced the International Freight Assistance Mechanism (IFAM). This was a temporary, emergency measure to help restore critical global supply chains which had been heavily impacted by COVID-19 containment measures around the world. Exports benefitting from this support included lobsters from Western Australia, Victorian lamb, and Tasmanian salmon. IFAM helped to ease pressures on animal production supply chains by maintaining the flow of high-value, time-sensitive, and perishable exports (29).

Concerns were raised about the live export of cattle and sheep, such as getting veterinarians and livestock handlers to the ships and home from international ports. If ship crew contracted the disease, or international borders or ports were closed, contingencies would need to be in place to ensure that the animals health and welfare could be maintained. In the event of canceled shipments, animals would need to be held for longer periods in quarantine feedlots until an alternate destination or domestic processing could be arranged (30).

In late May, the MV *Al Kuwait* livestock carrier arrived in Freemantle Port, Western Australia, with 12 crew members infected with COVID-19 (31). By 2 June, 21 members of the 48-person crew had tested positive to COVID-19, causing the export of 56,000 sheep to the Middle East to be postponed (32). The Australian Federal Government Department of Agriculture, Water and Environment rejected the exporter's initial request for an exemption to the Northern Summer Order, which prohibits live export of sheep by sea to the Middle East during the months of June to mid-September. However, the voyage was later approved to embark subject to a number of conditions; this decision recognized the "exceptional circumstances resulting from the global COVID-19 pandemic" (33).

Pork and Chicken Meat Production

A major welfare concern for intensive livestock industries, such as pork and chicken meat production, was the risk of disruption to the supply chain if personnel in the supply chain contracted the virus. Concerns included shortages of feed and other supplies, shortages of staff to maintain animal care, and reduced processing capacity, causing overcrowding and a backlog of animals at farms. The latter could lead to the need for the humane destruction of animals on farm. Pigs and broiler chickens were identified as being particularly vulnerable because of their targeted weight gain and the potential for health problems if they are not slaughtered at the scheduled age. Because these production systems operate as a continuous supply of animals, a disruption in slaughter capacity would result in over-production. Broiler chickens reach slaughter age at 30–60 days, so it takes about 2 months to reduce production levels (34). For pigs, the oversupply would last at least 3 months before systems would reach a new steady state at reduced supply, and if the supply was reduced, it would also take several months to return to normal production levels (35).

In the state of Victoria, the second wave of COVID-19 infections in June led to a 34% reduction in meat processing capacity because of measures to avoid the overlap of shifts and to ensure physical distancing (36). When the processing capacity in Victoria was impacted, then the Governments of Victoria and South Australia (SA) arranged for pigs and broilers to be transported across the SA border, and to be processed in SA. The pork industry was relatively well-prepared for the changes in processing capacity, because emergency preparedness plans had been established due to the threat of an incursion of African Swine Fever. Much of the pork industry had strict biosecurity measures in place and had the capacity to isolate animals. Pork processing establishments had the ability to close at short notice. Australian Pork Limited (APL) communicated with pork producers to determine that there would be an extra 2 weeks reserve space on farms to handle the backlog of pigs that would be caused when processing capacity was reduced. APL also investigated the fast tracking of research on humane methods for the mass killing of pigs. In other countries, for example the United States, the closure of meat processing facilities led to hundreds of thousands of pigs and chickens being humanely destroyed (37, 38), but this did not happen in Australia.

Eggs, Milk, and Wool Production

In livestock sectors where products are harvested on farm, such as in eggs, milk, and wool production, the main concerns during the COVID-19 pandemic were about possible interruptions to the feed supply chain and reduction in workforce capacity. Australian Eggs urged egg farmers to review their access to supplies and to identify any supply chains that might be jeopardized due to national or state restrictions related to the pandemic (39). Representatives from Australian Dairy Farmers, Australian Dairy Products Federation, and Dairy Australia worked to ensure that dairy activities were classified as an "essential service" and implemented measures to keep supply chains operating (40).

In the wool industry, shearers normally travel within Australia, and from New Zealand to Australia, for seasonal shearing and crutching (removal of the perianal wool). The restrictions on international and domestic movement meant that shearers could not travel. Shearing and crutching are done for production purposes but are also critical to the welfare of sheep. Specific welfare risks of not being shorn include build-up of moisture, urine, and feces in the wool, which can lead to fleece rot and flystrike, wool blindness, and skin irritation and infections (41). The wool industry requested visa exemptions for New Zealand shearers and produced guidelines to reduce physical contact during shearing. As of September, the request for exemptions had not been granted.

Aquaculture

The aquaculture sector was impacted by major market shifts during the COVID-19 pandemic, which were caused by the closure of restaurants and catering services and a reduction of export capacity. At the start of the pandemic, there was some concern that these shifts in market demand could cause financial constraints for producers, who then might not be able to pay for veterinary investigations and feed, which could result in poor health and welfare outcomes (42). Similar to the situation with the pork and chicken supply chain, there was a risk of oversupply in the aquaculture supply chain, which could impact animal welfare. Finished aquaculture stock might not be able to be moved off farm, because aquaculture commonly uses ponds and sea cages that cater for a finite volume of stock.

As the food service and export markets contracted, the aquaculture sector quickly shifted their sales channels to meet the increase in demand by Australian consumers, who began cooking more from home during the COVID-19 pandemic (43). For example, Barramundi farmers urged consumers to buy Australian barramundi (44). By May, international air freight had expanded, partly due to the Australian Federal Government establishing an International Freight Assistance Mechanism (29). With the increased ability of the sector to access international markets, pressure on the supply chain eased.

Zoos and Aquariums

In the early stages of the pandemic, zoos and aquariums saw a loss of income due to forced closure to the public, which put at risk their ability to provide appropriate care to the exhibited animals. Zoos and aquariums rely on gate entry fees to finance the cost of animal care (e.g., electricity for temperature control and water quality/life support systems, costs of feeding, costs of maintaining animal enclosures, costs of veterinary care and treatment). Without such income, zoos and aquariums had to draw on reserves as well as significantly realign expenditure to sustain appropriate care. Some facilities estimated 8 weeks of resources remained before they would need to permanently close. Normally when a facility closes, animals are relocated to other facilities, but during the COVID-19 pandemic, relocation was not possible because neither the sending nor receiving institution had the financial resources for relocation costs or the care of additional animals. There was concern that pressures to sustain animal care across multiple facilities may lead to difficult decisions. In other countries, the humane destruction of exotic and native animals was being openly considered (45).

Members of the Zoo and Aquarium Association (ZAA) in Australia participate in vital conservation programs, conduct wildlife rescue, and participate in a number of Australian Government Threatened Species Recovery programs. As conservation businesses, they play an important role in the protection and welfare of Australian native species, and a role in rehabilitation and species recovery after the summer bushfire season. Threats to the viability of zoo and aquarium businesses posed by the COVID-19 pandemic put this important work at risk.

When zoos and aquariums were closed to the public, a welfare issue was identified in the reduction of human interaction with the animals. The human-animal relationship is important to the welfare of some captive animals (46), and various zoos and aquariums reported signs of negative affect in their animals during the closure period. For example, Cairns Aquarium observed that larger species, particularly Maori wrasse and Queensland groupers, exhibited depression-like signs, such as refusal to eat (47).

The risk of human-to-animal transmission of SARS-CoV-2 was highlighted by sporadic reports abroad (48). Precautions were taken by zoo and aquarium personnel and veterinarians to minimize contact with animals at high risk, such as large cats and primates. No incidents of SARS-CoV-2 transmission between humans and animals have been reported in Australia.

Given the importance of the sector to tourism, on 28 April, the Australian Federal Government released a $94.6 million package to ZAA accredited zoos and aquariums, and other wildlife businesses, to support the ongoing provision of animal care (49). Non-government zoos and aquariums could apply for the Federal Government JobKeeper program to assist with staffing costs (50). In addition to the support package from the Australian Federal Government, some jurisdictions provided financial support to smaller businesses, with grants administered by state tourism or development agencies (51–53).

Prior to the announcement of the support package from the Australian Federal Government, ZAA had explored animal feed solutions with other animal industries (e.g., the meat processing sector), where collaboration would reduce the cost of care for animals at zoos and aquariums. The use of trucks and provision of whole carcasses at a reduced cost were sought to assist in maintaining animals' care. Following the release of the Australian Federal Government support package, ZAA continued to explore opportunities to reduce the costs of care, because it was recognized that zoos and aquariums might have reduced visitation in the medium term.

Wildlife Parks and Mobile Exhibitors

Like zoos and aquariums, wildlife parks depend on visitors for revenue. Some wildlife parks did not qualify for grants under the Australian Federal Government support package, but most retained their employees through the Australian Federal Government JobKeeper program. Many wildlife parks received food donations, and others started online crowd funding campaigns (54). As for zoos and aquariums, the animals in wildlife parks probably experienced loss of the enrichment that is normally provided by the interaction with visitors.

Wildlife mobile exhibitors (such as petting zoos and mobile farms) were significantly impacted by the closure of schools and the banning of gatherings such as birthday parties. When public schools re-opened, many exhibitors were still prohibited from entering schools. Because country shows (fairs) can provide up to 70% of the income for some operators, the cancellation of country shows had a significant impact on many wildlife mobile exhibitors. While mobile exhibitors could not access the Federal financial assistance that was provided to the zoo and aquarium sector, some jurisdictions did provide assistance (51, 52). For example, the Queensland Government provided a $0.5 million grant to support the licensed mobile sector. The rationale for that support was that the mobile exhibitor sector in Queensland contributes toward awareness and education of Australia's native species (51). When public schools re-opened, many exhibitors were still prohibited from entering. During this time, the animals in mobile shows were maintained, but many operators faced significant financial issues.

Wildlife Rescue and Rehabilitation

When the COVID-19 pandemic began, most wildlife rescue organizations were recovering from the impacts of the summer bushfires, which devastated large portions of habitat in eastern and south-eastern Australia (55). Some rescue organizations had financial reserves from bushfire donations. Their ability to collect additional donations, or accept volunteers, was limited, which increased the workload and created the need for alternative feed supplies.Wildlife Health Australia (WHA) was concerned that the COVID-19 crisis could impact animal welfare if workers could not attend to the needs of the wildlife in their care, or free-ranging wildlife under their management (e.g., threatened species programs). WHA highlighted the necessity for people in wildlife care and emergency response roles, both paid and voluntary, to be recognized as "essential workers" by governments (56). WHA also encouraged those who care for wildlife to develop contingency plans in the event that they became sick or had to self-isolate (57). There were also potential impacts on conservation and welfare when wildlife research was discontinued due to public health concerns or financial constraints related to COVID-19.

In some other countries, concern about the potential risk of transmission of COVID-19 from humans to wildlife, particularly bats, resulted in the suspension or restriction of rehabilitation and research (58, 59). Similar concerns were raised in Australia, alongside concerns about the negative welfare impacts if restrictions were imposed. WHA worked with government and non-government stakeholders to assess the risk within the Australian context and to provide advice on biosecurity measures to minimize the risk of transmission while rehabilitation and research continued (60). One positive impact of the COVID-19 pandemic, as a result of the decrease in international travel, may have been a reduction in the lucrative, illegal smuggling of wildlife out of, and into, Australia (61). Reduced traffic through national parks and other wildlife areas likely reduced roadkill and disturbance of animals, but it might have also increased opportunities for smugglers to collect animals undetected.

Horse and Greyhound Racing

Horse and greyhound racing continued throughout Australia during the pandemic, except in the state of Tasmania (62). Betting continued online, but revenue from on-course betting, gate takings, restaurant and bar services, and stud fees all decreased because of both the economic downturn and the restrictions on attendance at the races. With reduced revenue from racing, there was a concern that horse owners would no longer employ trainers and veterinarians. If trainers were not being paid, they could return horses to their owners, who may not have the facilities, knowledge, or capacity to care for them. The capacity to rescue unwanted horses was also reduced, as horse rescue groups experienced a decrease in donations and were unable to run fundraising events.

Although greyhounds are less expensive to maintain than horses, the greyhound industry was affected financially by the COVID-19 pandemic. Greyhound racing continued under strict COVID-19 containment protocols that were quickly implemented in each jurisdiction, including fewer staff on track, limited participant attendance, the regionalising of race-day officials in some jurisdictions, and the implementation of strict pre-entry health checks. Some jurisdictions also moved to a regional racing format, for a period, where participants were required to race within specific regions. Border closures limited the ability of some greyhound owners and trainers to cross state borders to access greyhound tracks. Despite income loss for some greyhound owners and trainers during this time, care for the animals was maintained.

Animals Used in Research and Teaching

When the pandemic started, research and teaching institutions responded in the first instance with a change to staffing processes. They divided their animal care staff into two teams, who worked alternate shifts to provide around-the-clock care for animals, as required by Australian laws, and to reduce the risk that an entire workforce would become infected. Access to animal houses was restricted to essential people. Teaching with animals ceased, but most research continued under modified conditions. Animal Ethics Committees (AECs) carefully scrutinized changes to protocols, and the contingency plans that had to be developed for each project. There was a reduction in breeding for animal colonies, where appropriate.

An initial concern was that research animals would have to be humanely destroyed if researchers were unable to access those animals in their experiments (63), but Animal Welfare Officers from major research providers have reported that very few animals were culled due to the cancellation of research projects. Research projects that had already commenced were permitted to continue once contingency plans were developed and approved. Non-urgent new projects were deferred. Many researchers were given a 12-month extension by their AEC for animal work that had not commenced.

In some research institutions, animal care staff took on research activities (such as monitoring) rather than have researchers attend, and researchers were taught basic animal husbandry in case the animal care staff were unable to work. In primary and secondary schools with animals, rosters were put in place to care for animals during school closure.

Companion Animals

In the early stages of the pandemic, there was concern that tight controls on human movement and the closure of borders would discourage people from seeking veterinary assistance, leaving home to care for animals (e.g., horses in agistment), or transporting supplies and animals. In March, some organizations, including Animal Health Australia (AHA), the Australian Veterinary Association (AVA), and the Royal Society for the Prevention of Cruelty to Animals (RSPCA) Australia, contacted the Australian Federal Department of Agriculture, Water and the Environment to request that veterinarians be classified as an essential service. The request was granted. The AVA also re-affirmed that veterinarians could conduct telemedicine consultations in the context of the COVID-19 pandemic (64).

Many animal shelters struggled financially due to the closure of charity shops and fundraising events that normally provide support for their work. At the beginning of the pandemic, RSPCA Australia led a "clear the shelter" campaign, which was highly successful in increasing pet adoptions, and non-RSPCA shelters reported an increase in pet adoptions. It was suggested that the government "stay at home" directions also might have motivated some people to adopt pets (65). There were some delays in pet adoptions, because the gonadectomization of animals was considered a non-essential surgery and was discouraged (although not prohibited) during lockdown (66). By late June, there had been some returns of animals to shelters, but the overall outcome was a net reduction of animals in shelters (67). Veterinarians reported a rise in pet behavioral issues (68), which might have been a result of the increase in adoptions.

Another consideration was how animal care could be sustained if a pet owner became sick or hospitalized. To deal with that risk, some city councils and shelters implemented networks of foster carers (69). There was concern that horse owners might be unwilling or unable to meet the expense of maintaining their horses if the owners lost income. A few cases of COVID-19 in dogs and cats were reported in different countries around the world (70), and there was concern that public fear of zoonotic transmission might cause people to abandon their pets. Several organizations provided information to the public to assert that pets were not considered at risk of contracting or spreading COVID-19 in households and the community (71). RSPCA Australia also provided information on advising pet owners on how to care for animals under the restrictions, how to keep citizens and their animals safe, and also to address potential welfare issues such as lack of socialization of puppies, behavioral and welfare issues when owners went back to work, and animals being scared by people wearing masks. RSPCA Australia also provided emergency resources for people on how to make plans for their animals in the case that they might get sick or be unable to care for their animals, either during the pandemic or for other reasons.

FORMATION OF A NATIONAL, MULTISECTORAL RESPONSE GROUP

On 24 March 2020, the Zoo and Aquarium Association approached The Animal Welfare Collaborative (TAWC), a collective of universities, organizations, companies, and individuals that was formed in 2018 with the common goal of improving the welfare of animals. ZAA sought information on how other animal sectors were responding to COVID-19-related challenges. TAWC responded by contacting the Australian Federal Department of Agriculture, Water and the Environment; Animal Health Australia; and the National Primary Industries Animal Welfare Research, Development and Extension Strategy (NAWRDES). On 27 March, TAWC, NAWRDES, and AHA created a national, multisectoral response group, called the COVID-19 Animal Welfare Response Reference Group (COVAWRRG). More than 34 organizations participated in the group, including the Federal, State and Territory departments of primary industries, animal protection organizations, the livestock production and processing sectors, the aquaculture, wildlife, and animal racing sectors, the zoo and aquarium sector, the animals in research and teaching sector, and the companion animal sector. The COVAWRRG met weekly during the early stages of the pandemic, and later fortnightly, to share critical sector updates on emerging COVID-19-related challenges to animal welfare, and to coordinate responses.

Within the first 2 months of the pandemic, key outcomes of the COVAWRRG included clarification on the regulation of the cross-border transport of animals, identification of the need to travel across state and intrastate borders to care for animals, and considerations for rapid-depopulation and culling in response to COVID-19 impacts on processing capacity. The need to classify veterinarians and other key personnel as an essential service, and to support zoos, aquariums, and wildlife parks in financial hardship were also key issues raised in the COVAWRRG. During the second wave of COVID-19, government statements and industry plans addressed animal welfare concerns with greater clarity than they did during the first wave, a preparedness that may have resulted in part from COVAWRRG discussions. For example, the statement by the Premier of Victoria on 3 August 2020 that indicated that Stage 4 restrictions were to be reinstated, specified that all agricultural, food production businesses, animal care, and necessary support services could continue to operate as normal. The emphasis on animal care could be attributed to the awareness of the issues that had been raised.

RECOMMENDATIONS FOR FUTURE CRISES

1. **National risk assessment –** There is a need for a national framework for risk assessment of animal welfare, across all sectors, to identify potential risks to animal welfare, not just animal disease risks.
2. **Clear communication channels –** There is a need for clear communication channels among industries and Organizations that deal with animals and their welfare, and for consistent, streamlined, and easy-to-access communication strategies for the public.
3. **Contingency plans for animal welfare –** Sectors that are responsible for the care of animals need crisis response plans in place, covering everything that could disrupt animal care. Risks include natural disasters, biosecurity events, supply chain shocks, Labor disruptions, movement restrictions on personnel, financial hardship, feed supply shortage, and limitations to transport and processing capacity. Contingency plans must cover financial hardship, and they need to identify resource reserves that can be used to ensure that the care of the animals is not compromised. Sectors should document the arrangements that were developed for the COVID-19 pandemic and incorporate these into contingency plans.
4. **Crisis response group** – In the event of a crisis that has not been forecasted, it is essential to quickly assemble relevant sectors to identify common issues, coordinate responses, exchange information and support, and develop appropriate solutions. The COVAWRRG might have been the first example of such a cross-sectoral crisis response group in

animal welfare. Ongoing collaborative partnerships among sectors will no doubt facilitate the assembly of a crisis response group in the future.

5. **Support systems for animal care providers –** Challenges to human mental health during a crisis may compromise one's ability to provide adequate care for animals or to perceive when animal welfare is at risk. Support systems for animal care providers during times of crisis should be developed by each sector.

CONCLUSION

The COVID-19 pandemic created angst and fear across society in addition to the health threats that it posed and touched all Australian sectors that care for animals. The spontaneous formation of the COVAWRRG, a national, multisectoral response group on animal welfare, facilitated the flow of information and helped to mitigate shocks to different sectors and to ensure the continuity of care for animals. The COVAWRRG provided a platform for communication and collaboration for 34 diverse organizations, including the Federal, State and Territory departments of primary industries, animal protection organizations, the livestock production and processing sectors, the aquaculture, wildlife, and animal racing sectors, the zoo and aquarium sector, the animals in research and teaching sector, and the companion animal sector. The activity of the COVAWRRG demonstrated that the responsibility for animal welfare is shared by multiple enactors across society, and therefore, multisectoral collaboration is an efficient way of addressing complex challenges in animal welfare (72). The experience of the COVAWRRG provides insight on mechanisms to ensure that animal welfare is not compromised during unpredictable events, such as the COVID-19 pandemic.

DATA AVAILABILITY STATEMENT

The original contributions generated for this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DB, JF, SM, and AT drafted the manuscript. All authors provided information and contributed to the editing of the manuscript.

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