VIEWPOINT: Human-animal interaction and the emergence of SARS-CoV-2

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VIEWPOINT: Human-animal interaction and the emergence of SARS-CoV-2

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Abstract

Given our long history of fighting outbreaks, which have proven to be an excellent reminder of myriads of pathogens with menacing potential of emerging, it is absurd that we are still taken by surprise when faced with a new one. In various ways, humans have actively contributed to the emergence of novel pathogens, including the cause of the current coronavirus disease-19 (COVID-19) pandemic. The intricacy of the dynamics of emerging diseases implicate a number of interconnected factors that reinforce contact between humans (hosts) and pathogen reservoirs, particularly animals. In light of the current COVID-19 pandemic and fears of second waves of infection, we call for re-evaluation of the human-animal interface.

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Reviewers comments	**Response to reviewers** We would like to thank both reviewers for the helpful and constructive comments. We have addressed each comment point-by-point. Moreover, to aid the review process, we are submitting two copies of the manuscript, one with track changes.
EDITORIAL COMMENTS (Decision: C)	
The title should denote that this is a viewpoint article.	This has been done as suggested.
The language used in the abstract should be more factual/subjective and less sensational. Explain what you mean by re-evaluating the human-animal interface. The abstract should stand on its own, not be a "teaser" for information in the full paper.	The abstract has now been re-written in its entirety taking into consideration these comments.
Add an introductory paragraph that introduces readers to COVID-19/SARS-CoV-2 and the current context of the pandemic at the time this viewpoint was written. This will be important for readers in the future who may not be as familiar with the current pandemic we are all currently living through.	As suggested, an introductory paragraph has now been added.
There should be some introduction to the structure being used in the viewpoint article. The question-based headings are okay, but you should pick either questions or topics and not both. The section topics should also be framed into a larger overall purpose for the viewpoint article in that introductory paragraph. This will help readers understand the relevance of the topics you detail and how they are related to one another.	We now summarized the structure used in the article in the introductory paragraph. All headings are now statement- based and consistent.
Figure 1 doesn't appear to help readers understand the concepts being portrayed. The graphical representation of these concepts is complex and the written explanations probably suffice for readers to understand the basic concepts. The main benefit is emphasizing the levels of transmission, but those are already very clearly described in the written text.	The section "*Revisiting the four levels of emerging infectious diseases*" was deliberately kept short to allow the inclusion of the figure. We strongly believe that the figure helps to reinforce the importance of the 4 levels of transmission. Interruption of transmission is after all the cornerstone of prevention and control of emerging infections that is discussed in our article.
I don't understand what the next steps are. The main call to action is too general to be useful/impactful. This is the only area where the viewpoint paper has any real potential impact on readers. Without it, the paper is just a summary of already very well-described zoonotic disease principles and recommended actions. Solely re-affirming those does not rise the level of a new published paper. The recommendations should be more specific/comprehensive. You should also address other previous international efforts to address similar issues, such as OneHealth.	Thank you for this point. We have now included a section entitled "*Recommendations*" highlighting some of the important measures that need to be implemented to prevent and control potential infectious diseases outbreaks. This has been done in the context of the One Health initiative.
Some references are incomplete or improperly formatted.	All references have been checked and updated.

Point-by-point response to reviewers

Point-by-point response to reviewers

Reviewer B: General comments: This paper is a nice effort to document the zoonotic importance of emerging pathogens Specific comments: This paper requires revision	
Major comments:	Thank you for this comment.

1. Paragraph 4. "Moreover, almost three-quarters of new human viruses have been due to cross-species transmission" Please clarify: -have been emerged due to cross-species? -Or viruses have a cross-species transmission?	This has now been rephrased and clarified.
2. Paragraph 4. " of persons one infected case can transmit to " could be changed as "Of secondary infections in naïve"..........	This has been changed.
3. Paragraph 7 is continuity of paragraph 6, delete heading "concluding remarks" and continue discussion as "adaptation in a short time [18]. Collectively, the above-mentioned factors................. 4. Needs a comprehensive conclusion of 5-7 sentences	These changes have now been incorporated and a new concluding paragraph is added
Minor comments: Few grammatical errors 4. Figure 1 description, 2nd last line "decrease" instead of decreases	This has been corrected. Other typographical errors have also been corrected.
Reviewer AF: This paper: well-described human-animal interactions	
General comments: No	
Specific comments	
Major comments	
Minor comments	

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Keywords: Zoonosis, human-animal interface, COVID-19, SARS-CoV-1, outbreaks

Abstract

The COVID-19 pandemic has affected all sectors of society, from health to economics, and from social to travel. The level and extent of this impact is unprecedented. Although the cause of COVID-19 was quickly identified to be a new coronavirus, the world was poorly prepared in preventing its spread. One important pillar of preparedness is surveillance of the sources of emerging pathogens and responding appropriately to prevent their spread in the human population. The ever-increasing interaction between humans and animals is one leading factor facilitating the emergence of new pathogens. In this perspective, we discuss the possibility of the zoonotic origin of SARS-CoV-2, the cause of COVID-19, and highlight the importance of understanding human-animal interaction to improve preparedness for future outbreaks.

Introduction

Currently the world is battling a pandemic caused by a virus, not previously recognized in humans. The new virus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified to be the cause of coronavirus disease 2019 (COVID-2019). The infection presented with a broad spectrum of symptoms ranging from mild disease, to organ failure and death. Similar to SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is a +ssRNA member of the β-coronavirus genus. However, relative to SARS-CoV-1, SARS-CoV-2 appears to be more efficient in human-to-human transmission [1,2]. The fact that global spread of the virus outpaced infection control measures has raised concerns about our preparedness to face new viral threats. In this viewpoint article, we discuss the potential zoonotic origin of SARS-CoV-2 and revisit the main elements that promote emergence and spread of new infectious diseases. We also highlight the factors that instigate the rise of new human pathogens and outline recommendations for prevention.

SARS-CoV-2 and the possibility of animal-to-human spillover event

Despite the uncertainty about where and when SARS-CoV-2 originated, the genome sequencing of isolates from early cases suggest an animal origin, with bats being suggested as the most probable source [3–6]. *In silico* evaluation of SARS-CoV-2 receptor, the angiotensin-converting enzyme 2 (ACE2), indicates that the current pandemic may be caused by a virus with a broad range of hosts, including, swine, civets, cats, cows, buffalo, sheep, pigeon and pangolins [7]. The susceptibility and permissibility of these animals, however, are yet to be tested and proven. One or more of domesticated and wildlife animals are proposed as an intermediate host for SARS-CoV-2, aiding the spillover to humans [8–11]. Determination of seroprevalence of SARS-CoV-2 and experimental infection of these animals will help to clarify which of these animals, if any, may be involved in the emergence of SARS-CoV-2 [5,7,12]. Moreover, it is also speculated that SARS-CoV-2 could be a result of recombination of two viruses that circulate in animals living or placed close to each other [13,14].

If SARS-CoV-2 is the result of a cross-species spillover, the conditions that facilitated the adaptation of SARS-CoV-2 to humans, remain unknown [15]. If pre-jump adaptation occurred in an intermediate host, then SARS-CoV-2 would have undergone genetic refinement in one or more animal species that were spatiotemporally aggregated, and in constant contact with humans. The intermediate species is likely to carry an ACE2 receptor that closely clusters with that of humans. If viral adaptation occurred after the spillover event, then continuous passage of the virus from person to person would provide the necessary natural selection opportunities. This would be a realistic assumption given the relatively long incubation (and infectiousness) period allowing for unnoticeable transmission, associated with respiratory route. The progeny virus, post-adaptation, can be somewhat genetically distinct from the original virus that made the initial animal-to-human jump [4]. For instance, examining cases of 2002 SARS outbreak revealed that, SARS-CoV-1 isolates from early cases (2002) differed from viral isolates obtained from later cases (2003). The viral spike (S) protein involved in binding to the ACE2 receptor, showed reduced binding affinity in later viral isolates compared to early isolates [16]. Additionally, a sequence of 29 nucleotides in the C-terminus of the viral genome was deleted in viral isolates from later cases and this deletion is believed to have occurred through viral adaption to human host [17].

Revisiting the four levels of emerging infectious diseases

The dramatic rise of human activities in animal farming, livestock and poultry industry, live-animal markets and bushmeat, has dangerously increased human-animal and animal-animal contact rate [18]. As a result, and combined with careless practices of animal handling, pathogen attack rate has surged substantially. Animals (wildlife and domestic) have gained a lot of attention as candidate reservoirs for numerous, often serious, emerging viral diseases including Monkeypox, Ebola, HIV, West Nile virus, rabies, and A/H5N1. The complex link between humans, animals, and emerging pathogens can be simplified to a 4-level model (Figure 1). At level 1 (or exposure), human host encounters the "new" pathogen (e.g. virus). Handling animals promotes such encounter. This initial encounter can happen independently of human's susceptibility to the virus. Susceptibility means that the host has suitable receptor(s) for viral attachment. It is unknown the number of viruses to which we are exposed, but given the profound interaction we have with our environment, we can only assume that the exposure is much higher than we possibly recognize. At level 2 (or infection), the human-virus encounter becomes fruitful. Human host becomes susceptible and composes part of the viral lifecycle. Over a thousand pathogenic species have successfully achieved this level. In fact, within the last four decades, new human pathogens have been identified at a rate of more than 3 annually. The majority of these pathogens were viruses [19]. This predominance of viruses as causative agents of emerging diseases is partially attributed to enhanced approaches in viral detection, and increased viral mutation rates occurring at relatively short spans [20]. Moreover, almost three-quarters of new human viral infections are attributed to viruses of animal origin that crossed species barrier [21,22]. Indeed, viruses of non-human primates and bats are associated with high relative risk of emergence [23]. At level 3 (or transmission) the new virus can spread from one person to another. This is generally indicated by the basic reproduction number (R_0); a measure that estimates the number of secondary infections in "naïve" susceptible population [24]. A pathogen with R_0 greater than 1 has better chances of widespread transmission leading to level 4. At level 4 (epidemic/pandemic spread), efficient human-to-human transmission generates sustained propagation. This usually happens without the need for new animal-to-human cross-species transmission events [25].

Factors that spark animal-to-human spillover

The cascade of events which led to the emergence of SARS-CoV-2 are likely to be complicated, but there seems to be a belief that humans at some point were exposed to the new virus, probably from bats directly (the reservoir?) [26], or indirectly through an intermediate and/or amplifying host(s) (wild and/or farmed animals) [5,27,28]. Indeed, increased aggregation of people, wildlife and domestic animals in spatiotemporal closeness, and various ways of handling animal products could have increased exposure rate (level1). In order to understand what could have precipitated this cross-species transmission (level 2), it is critical to identify the reservoir and intermediate hosts. The intermediate host can act as a biological bridge between the reservoir and humans. Despite active infection, intermediate host may appear healthy or asymptomatic long enough for the virus to jump unnoticed to humans. The intermediate host offers the virus an additional advantage of a suitable environment for rapid evolution priming for the jump from animal species to humans. Post-jump changes in the virus also tend to occur in the human host, and the significance of these changes is yet to be unraveled [29].

In addition to intermediate hosts, the reservoir is a key player in pathogen emergence. Fruit bats have been a common source for a broad range of viruses associated with emerging human infections [30,31]. In the beginning of the 1990s, humans who came in close contact with the blood or body fluids of sick infected horses (intermediate), acquired new a virus, known as Hendra virus. Later, fruit bats were found to be the source for this paramyxovirus. Since then, Hendra virus has caused some isolated outbreaks of serious and often fatal infections in horses and humans [32]. Moreover, in a single outbreak in 1997, Menangle virus, another paramyxovirus circulating in bats, spilt over to pigs. Humans working in pig farms were directly exposed to the virus shed in the secretions of infected pigs, or indirectly through contaminated surfaces [33]. Fruit bats appear to harbor viruses with broad host range; viruses that utilize cellular receptors that are highly conserved across species providing better chances of breeching species barrier [34,35]. For example, Nipah virus, a new human pathogen was recognized in 1998 in association with pig farming and cases of fatal encephalitis. In addition to humans and pigs, the virus could naturally infect other species including horses, dogs and cats [36]. Thus, these animals also became hosts for the virus. Although pigs were the intermediate host in the early outbreaks of Nipah in Malaysia and Singapore, more recent outbreaks in India and Bangladesh suggest direct transmission from bats to humans through contact with fruits contaminated with bat infectious fluids (e.g. urine, saliva) [37]. Interestingly, numerous RNA viruses circulate in bats. RNA viruses are a predominant cause of newly emerging zoonotic diseases, such as Ebola and SARS-CoV-2. Accelerated rates of mutation and presence of several variants of a given strain, provide RNA viruses with unmatched capacity of rapid adaptation in short time [20].

Collectively, the above mentioned factors explain how activities pertaining to human-animal interface pose an increasingly high risk of pathogen emergence. We may not have substantial evidence for the involvement of human-animal contact in the emergence of SARS-CoV-2, but the new outbreaks in mink farms in the Netherlands [38,39] certainly highlights how cross-species transmission could occur. Indeed, this possibly bidirectional spread between humans and animals necessitates policies that regulate human-animal contact. Furthermore, expanded human population has led to increased wildlife hunting, bush meat, live animal markets, densely populated livestock and poultry industry, exotic species trading and rapid animal transportation, to meet the growing demand for such products. This has created continuous and intense contact between humans, and potential viral reservoirs, vectors and intermediate hosts. Additionally, with increased human movement at exceptionally accelerated speed, pathogens can be introduced to previously uninfected areas, which are geographically distant from the source of infection leading to disastrous pandemics across the globe. Given that we do not have vaccine and immunity against most of the emerging viral diseases, resources directed at level 1 (i.e. exposure) remain our best hope to prevent costly consequences. It is believed that emerging zoonotic diseases involve a complex interaction between multiple anthropogenic factors that modify the structure and dynamics of wildlife [40].

Recommendations

Recognizing the importance of these factors has led to intensive collaboration efforts between different sciences and disciplines including, veterinary medicine, public health, environmental sciences and social sciences, among others. This holistic approach known as One Health has shown promising results in curbing the spread of pathogens between humans and animals and between animals and animals [41] . For instance, the integration of veterinary sciences, epidemiology and virology has led not only to the identification of the different animal reservoirs for rabies, but also to the establishment of surveillance systems for monitoring outbreaks and the development of an effective vaccine [42]. These outcomes led to significant improvements in the control of rabies in both animals and humans. Similarly, a vaccine against Hendra virus helped control infection in horses, and hence prevented transmission of the virus to humans [43]. Another example of fruitful multidisciplinary experience is monitoring the climate change to identify temperatures that favor pathogen transmission. For example changes in climate, which in turn can affect mosquito movement, has been used in prediction models to monitor the emergence of West Nile virus [44].

Although in principle, the One Health approach has been shown to be effective in controlling and preventing infectious diseases outbreaks, in reality, implementing it has proved to be challenging. Factors such as poor investment, lack of collaboration, and sub-optimal surveillance systems, have all hindered achieving the optimal outcomes [45]. However, continuous progress in the One Health approach and supporting policies, remain an essential shield in the face of future outbreaks [42]. This means serious efforts to improve and implement:

1) Continuous surveillance of animals and vectors (e.g. bats, rats, wild birds, primates, arthropods) for the emergence of new pathogens. This should help predict and prepare for the next pathogen threat and define regions susceptible to outbreaks and tools necessary to interrupt route of transmission. Additionally, further modelling, analyzing and estimating the risk of emergence can help prepare suitable diagnostic tools for rapid capture of a new outbreak, and frame essential mitigation protocols [46].

2) International cooperation to establish pathogen sequence libraries and databases updated with biological characterization of new pathogens. This can facilitate efforts in diagnosis, contract tracing and potential vaccine development.

3) Studying and monitoring human behavior associated with increased risk of emerging diseases such as wildlife trade and bush meat consumption. Social sciences are important to help introduce behavioral modifications that can be beneficial and easily adhered to by communities. This also requires education and increase in public awareness to the dangers of high-risk behavior.

4) Monitoring alterations in land use, climate change and air quality, as well as introducing policies to reduce and/or mitigate ecological consequences [42]. Zoonosis is greatly impacted by changes in land use. These changes impact the natural habitat of wild animals and their biodiversity, influence their breeding sites and determine the exposure rate of humans to pathogens in wild animals. Maintaining the biodiverse pool of wildlife and the natural habitat of wild animals should be a priority when planning landscapes [47].

5) Monitoring and implementing better, safer and sustainable animal agricultural practices. Overcrowding, mixing of animals, overuse of antibiotics and methods of transport, are some of the drivers of emergence and re-emergence of pathogens.

Conclusion

Humans share a close relationship with animals and their environment. Hence, the risk of emergence of new pathogens that can spillover into the human population cannot be completely eliminated. However, understanding the importance of the human-animal-ecosystem interface and tackling the diverse factors that influence the emergence of new pathogens is essential for better prevention, control, and mitigation. The

One Health approach could have significant positive impact in combatting the emergence of infectious diseases. However, this requires national and international cooperation, sharing of data, funding, implementation of policies and legislation, and political will.

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Supplementary Files

Manuscript with track changes.
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Figures

Four-level model of pathogen emergence. Bush meat production, poultry and livestock industry, live-animal markets warrant frequent close contact between animal-human and animal-animal and exposure to pathogens circulating in different species. Frequent exposure (level1) can turn into productive infection (level2), given the necessary viral adaptation has taken place to make us susceptible. By passaging through humans, the new virus may undergo further adaptation. Pandemic emergence necessitates an efficient human-to-human transmission for a sustained propagation. Fast human movement across the globe amplifies the chain of transmission. Efforts should be direct at preventing level 1 (exposure) to significantly decrease chances of pathogen emergence.