Real Science Review: Zoonotic Diseases

Student, Daniel Davidson: Ms. Ribardo, I am so confused about how this COVID-19 epidemic got started. Can you help me understand this?

Ms. Ribardo: That's a really good question, Daniel. I guess the first thing to know is the geographical location where the disease first appeared. In this case, this seems to be in the city of Wuhan, China. The next thing to know is if there is something unusual in that area that might serve as a source of infection. In this case, a wild animal source of the disease was suspected, because this city has many unsanitary meat markets that sell wild animals that are slaughtered at the market. You are going to review a research report that examines the likelihood that this might explain the origin of COVID-19. Does it matter how this disease got started? Think about it.

Original Report: Morens, David M. et al. (2020). The origin of COVID-19 and why it matters. Am. J. Trop. Med. Hyg. 103(3), 955-959.

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Vocabulary Used in the Original Report

Angiotensin-converting enzyme 2: an enzyme in the cell membrane of cells. When certain viruses bind to this enzyme, they break through the membrane to enter and infect the cells.

Cell Membrane Receptor: naturally occurring specific molecules, embedded in cell membranes, that can be bound by infectious agents, enzymes, hormones, drugs, or other compounds in ways that alter membrane permeability and cell function. The alterations may be helpful or harmful to cells, depending on the substances being bound.

Endemic (en-ˈde-mik): belonging to or native to a given species or location.

Epidemic (e-pə-ˈde-mik): outbreak of a disease that affects many people at more or less the same time

Epizootic disease: an animal disease that can cause epidemics or pandemics in different species, including humans

Genetic sequencing: determining the order of nucleic acid pairs (adenine- thymine, cytosine-guanine) pairs in DNA

Pandemic (pan-ˈde-mik): outbreak of a disease that affects many people in multiple countries and continents

Pangolins (paŋ-gə-lən): armadillo-like animals prevalent in Asia and Africa.

Taxonomic groups: animal or plant groups having natural relations. Such groups, in descending order, include kingdom, subkingdom, phylum, class, order, family, species, strains.

Origin of COVID-19 and Why It Matters.

Abstract

The COVID-19 pandemic is among the deadliest infectious diseases to have emerged in recent history. It is so contagious that it has caused disease all over the world. As with all past pandemics, we do not really know how it emerged. However, a wide variety of data sources indicated that the causal virus (SARS-CoV-2) evolved from a group of genetically related viruses that naturally affect bats and pangolins in Asia and Southeast Asia. For decades, scientists have warned that there is a high risk that this family of viruses can spawn new genetic viral strains that could repeatedly trigger new pandemics. We need some better ways to prevent and control such outbreaks. Those efforts will require more effective public health and society actions, as well as funding for new research. In the case of this COVID-19 pandemic, detection and control efforts were inadequate to stop the rapid and widespread infection.

In 2007, scientists studying coronaviruses warned: “The presence of a large reservoir of SARS-CoV–like viruses in horseshoe bats...is a time bomb. The possibility of the re-emergence of SARS and other novel viruses...should not be ignored” (ref.).

The SARS epidemic died out for reasons unknown, but now, 18 years later, a new virus SARS strain, COVID-19, has emerged as the deadliest respiratory disease pandemic since 1918 (ref.). The 1918 pandemic killed an estimated 50 million people. We need to prevent such pandemics from occurring again and at least control such outbreaks more effectively.

EMERGENCE OF THE COVID-19 PANDEMIC

The agent of COVID-19, SARS-CoV-2, was named after the genetically related SARS-CoV (more recently distinguished by some as SARS-CoV-1), which caused a deadly near-pandemic in 2002–2003 (ref.). Before 2019, neither SARS-CoV-2 had not been identified in either animals or humans, and its gene sequence was not known.

HOW VIRAL DISEASES EMERGE

Viruses are compact packages of DNA or RNA (COVID-19 is a RNA virus) that contains some proteins and a few lipids. Viruses are not living organisms in the sense that they can only survive by living inside living cells with the capacity to help the virus reproduce its nucleic acids and proteins.

Virus can switch host species. For example, viruses may leave insects to infect bats, and then leave bats to infect humans. Susceptible species are specific and limited in number. Most of the human viral and nonviral infectious diseases that have existed for centuries—measles, influenza, cholera, smallpox, falciparum malaria, dengue, HIV, and many others—originated by animal-to-human host-switching (refs.).

How Viral Diseases Emerge: Questions to Answer

1. Host switching has to involve the ability of an infectious microbe to penetrate cells of a different host species. How might cell membranes be involved?
2. What are common features of the countries expected to be future sources of zoonotic outbreaks (Fig. 2)?
3. What is the value of knowing which countries will be likely sources of future outbreaks?

Factors that influence host switching include opportunity for exposure, the environment, and biology of the species involved. The relevant biology includes genetic similarity and behaviors that increase exposure between species.

A well-understood example is influenza virus emergence into humans and other mammals (ref.). Human pandemic and seasonal influenza viruses arise from viruses of wild waterfowl and shore birds. From within this natural reservoir, the 1918 pandemic virus somehow host-switched into humans. We know this from genetic studies comparing avian viruses, the 1918 virus, and its descendants, which cause annual seasonal influenza and have caused three pandemics. Similarly, other avian influenza viruses have host-switched into horses, dogs, pigs, seals, and other vertebrates (refs.), with as yet unknown potential to cause pandemics.

Coronaviruses are globally distributed in a large but unknown number of animal species. Human SARS-CoV and SARS-CoV-2 are closely related to numerous bat and pangolin coronaviruses in a viral genetic grouping called sarbecoviruses (Figure 1, not shown here)(refs.). Four endemic human coronaviruses, which emerged at some undetermined time in the past, cause mostly mild self-limited upper respiratory tract infections.

RECENT CORONAVIRUS EMERGENCES FROM ANIMALS INTO HUMANS

Until recently, relatively little was known about corona viruses. Eighteen years ago, a previously unknown coronavirus named SARS-CoV suddenly emerged. Following its initial appearance in China, it spread to 29 other countries, causing a near-pandemic and killing 813 of the 8,809 people with confirmed infection before being controlled by aggressive public health measures. It has not been seen since.

In 2012, however, another previously unknown coronavirus named Middle East respiratory syndrome coronavirus (MERS-CoV), and closely related to SARS-CoV, emerged to cause high case-fatality human infections. Fortunately, this virus does not spread efficiently between humans. Cases have been largely limited to the Middle East where its host reservoir, the dromedary camel, is present in relatively high numbers.

In 2016, yet another novel bat-origin coronavirus emerged in China to cause a novel epizootic disease in pigs, termed swine acute diarrhea syndrome coronavirus (SADS-CoV). And most recently, at least as early as late November 2019, SARS-CoV-2 was recognized, making it the third known fatal bat virus–associated human disease.

Over the past 15 years, scientists have identified animal reservoirs of corona viruses in Africa, the Americas, the Middle East, Asia and Southeast Asia, and particularly China. China is home to bats of more than 100 species, many of which carry coronaviruses. Based on the endemic distribution of various strains of coronaviruses, we can expect outbreaks of host-switching spread to arise in certain countries (Fig. 2)(ref.). A high risk for new pandemics exists from numerous human–animal interactions: bat tourism, wet markets, wildlife supply chains for human consumption, land management practices, and environmental disturbances (refs.).

Questions to Answer: Coronavirus Emergences

1. What do the words “infectious” and “contagious” mean?
2. When a “new” infectious disease suddenly appears in humans, what are the possible causes for its coming into being? Are there possibilities other than spread from infected animals?
3. What is suggested by the fact that a given virus appears in the same mammalian species (such as rodents, pigs, or cats) in countries of different continents, even if these animals cannot travel between continents?
4. How can we know if an animal virus can exchange hosts, including spreading to humans?

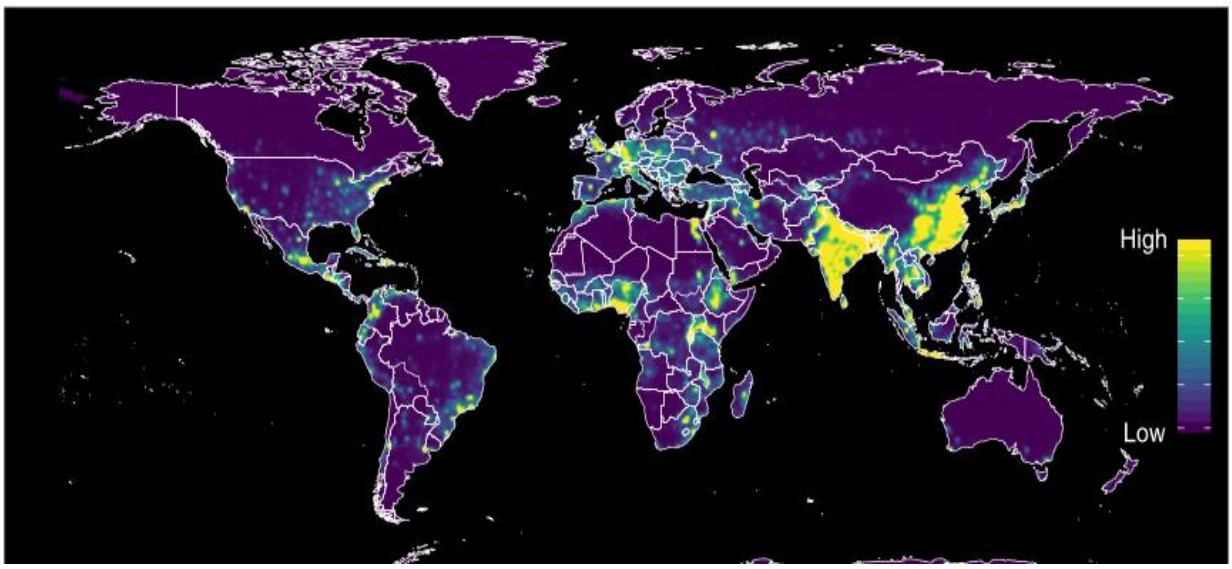

Fig 2. Areas of the world where disease emergence seems most likely to occur. Level of likelihood is indicated by the yellow color coding (reference cited).

CORONAVIRUS EMERGENCE RISKS

The risks of future coronavirus outbreaks are largely determined by the animal reservoirs of infection. Bats of numerous globally distributed genera and species are now known to be the major reservoir of animal coronaviruses. One 20-country study of more than 19,000 animals (predominantly nonhuman primates, bats, and rodents) revealed that bats accounted for more than 98% of coronavirus detections. Almost 9% of > 12,000 randomly studied bats were infected with one or more coronavirus (ref.). Bats of some species co-roost with bats of other species, facilitating viral exchanges and enhanced viral. In one study, more than 780 partial coronavirus gene sequences were identified from bats of 41 species infected by coronaviruses. Within the sarbecovirus family that included SARS and SARS-like viruses, many identified genetic sequences are very similar to SARS-CoV and SARS-CoV-2. One such virus is more than 96% identical to SARS-CoV-2 in its whole genome**. A**nother virus shares more than 97% identity in two genes (refs.)**.**

Questions to Answer: Emergence Risks

1. How can we use the knowledge of which animal species carry a potentially zoonotic disease to prevent or control outbreaks?
2. What are the responsibilities of governments of countries where reservoirs of infection exist?
3. Both bats and pangolins feed almost solely on insects. What are the chances that insects are a primary source of coronavirus infection?
4. What are the possible consequences of SARS-like viruses being able to bind to human angiotensin-converting enzyme-2 (ACE2) receptors in cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines. How could that help explain why older people are more vulnerable?
5. How can we use the knowledge of which animal species carry a potentially zoonotic disease to prevent or control outbreaks?

A bat coronavirus "hotspot" area includes parts of south/southwest China, Laos, Myanmar, and Vietnam. A rich diversity of SARS-like viruses has been found in these countries.

Many of these SARS-like viruses bind to human angiotensin-converting enzyme-2 (ACE2) receptors. This enzyme is attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines. SARs viruses infect human respiratory epithelial cells in vitro, suggesting their pandemic potential (ref.). Bat-to-human transmission of SARS-like viruses has already been detected (ref.), perhaps representing pandemic near-misses. Even the more genetically distant SADS-CoV infects cells of humans and numerous other vertebrates, raising concern about indirect coronavirus emergences. This seems to have occurred with the bat-to-camel-to-human emergence of MERS, and possibly with SARS-CoV emergence into humans, which may have resulted from bat virus infection of masked palm civet cats, with subsequent human spillover (ref.).

In 2017, the therapeutic benefit of the antiviral drug remdesivir was suggested. In 2020, this drug is widely used to treat persons infected with SARS-CoV-2 (ref.). Since 2007, when alarming predictions about threatened coronavirus emergences began to appear (ref.), understanding of coronavirus ecosystems has become far more complete.

Over the past 5 years, Chinese, American, European, and other scientists have begun to renew warnings based on the facts that:

- Humans are intensively interacting with coronavirus-infected bats,
- SARS-related bat coronaviruses have all of the essential components of the SARS virus,
- Some of these SARS-like viruses can infect laboratory-humanized mice to cause SARS-like disease,
- SARS-like viruses can directly infect and transmit among humans (refs.)

Many scientists in many countries have proposed aggressive monitoring of known hotspots to try to predict and prevent viral emergence that might impact human health (refs.). Unfortunately, outside of some members of the scientific community, there has been little interest and no sense of urgency. In 2020, we learned, tragically, what 12 years of un-heeded warnings have led to: the emergence of a bat-derived sarbecovirus—from the very same SARS-like bat virus group we had been warned about by multiple voices for over a decade. The infections were caused by a bat coronavirus that spread to humans from an intermediate host such as a Malaysian pangolin or another, yet-to-be-identified mammal (refs.). Theories about a possible man-made origin of SARS-CoV-2 in the Chinese research lab that studies coronaviruses have been thoroughly discredited by multiple coronavirus experts (refs.). SARS-CoV-2 is unlike any previously identified coronavirus from which it could have been engineered. Also, the way the Covid-19 virus binds to its human enzyme target is novel.

It is highly unlikely that SARS-CoV-2 was released from a laboratory by accident. No laboratory had the virus nor did its genetic sequence exist in any sequence database before its initial GenBank deposition (early January 2020). China's laboratory safety practices, policies, training, and engineering are equivalent to those of the United States and other developed countries (ref.), making "escape" from a research lab unlikely.

COVID-19 EMERGENCE MECHANISMS: REDUCING EMERGENCE

The pre-existing conditions for zoonotic infection and spread can be thought of as an "accident" of nature. We do not know what the molecular conditions for such infection and spread are. But we suspect that the conditions involve the similarities of a certain receptor (ACE2) on the cells of numerous mammals (bats, humans, minks, cats, and other domestic and wild animals)(refs.). The possibility of new pandemics is increased by the ability of coronaviruses to evolve at a high rate and the large array of wild animal species that can serve as hosts. We are already seeing coronavirus mutants with altered affinity for human ACE2.

Because bat sarbecoviruses so easily switch between multiple hosts, we face a many-pronged human risk. Because we have only just begun to sample, sequence, and study bat/mammalian coronaviruses, we can be certain that what we now know is but the tip of a very large iceberg. The findings described earlier reaffirm what has long been obvious: that future coronavirus transmissions into humans are not only possible, but likely. Scientists knew this years ago and raised appropriate alarm.

Our prolonged deafness now exacts a tragic price. The story of COVID-19 emergence sends a powerful message. A quantum leap in bat coronavirus surveillance and research is urgently needed. This work must emphasize:

- Virologic and behavioral field studies of humans and animal interactions, especially in disease hotspots (ref.).
- Expansion of important research that has been delayed, underfunded, or discontinued.
- More scientists, including scientists working in China and other hotspot countries, should be recruited to these efforts, especially in international research partnerships.
- Full, open international collaboration involving many countries is essential. In particular, field research on the prevalence and virus-host relationships of coronaviruses, development of technologies for diagnostics, vaccines, and animal models for studies of pathogenesis and potential therapeutics. Such research should include modeling the structure and functional binding relationships of virus and host receptors.

There are things that we can do now to lower our risks. We know much about coronavirus hotspots, not only in China but also globally. We can be more aggressive in monitoring these locations. We can also modify how human behaviors bring them into contact with bats. This includes changes practices in wet markets, bat cave tourism, capturing and eating bats, and perturbing the environment in ways that alter bat habitats and habits. These are behaviors that we can and must change.

We can also strengthen basic public health, including hygiene and sanitation, so that emerging viruses are less able to reproduce. Organizations like the Coalition for Epidemic Preparedness Innovations, among others, should be extended and strengthened, to emphasize vaccine development, therapeutics, and prevention tools. We must build and maintain strong public health infrastructure to respond quickly and efficiently to pathogen emergence.

For viruses that have emerged, such as SARS-CoV-2, we need to develop effective antiviral drugs and, ideally, broadly protective vaccines. We should begin developing broadly protective vaccines and broadly therapeutic antiviral/antimicrobial agents against pathogens within taxonomic groups likely to emerge in the future. Such groups include coronaviruses, henipaviruses, and filoviruses.

Education and communication with populations where spillover events occur are also an important component of risk reduction.

We must also realize that the problem is larger than just coronaviruses. In recent years, we have seen emergences and reemergences of numerous other human infectious diseases such as Ebola fever, Lassa fever, hantavirus pulmonary syndrome, human monkeypox, HIV, dengue, chikungunya, Zika, and epizootic avian influenza.

Questions to Answer: Reducing Emergence

1. If coronavirus infects by binding a certain membrane receptor (ACE2), what kind of drug research does that suggest we need to be pursuing?
2. What must we do about bats, besides just keep track of their coronaviruses?
3. What can humans do to reduce the spread of infections among humans?
4. What role is played by the ease with which people travel around the world? What should we do to reduce the disease-spreading nature of travel?
5. How can we convince people who reject vaccination to change their minds?
6. What preparations are needed to improve manufacturing and distribution of protective equipment, medication, and vaccines in future emergencies?

We have entered a new pandemic era (ref.) Epidemic and pandemic emergences are becoming commonplace; some are likely to be dangerous. In 2020, our science is sufficiently robust to have a good chance of controlling pandemic viral emergences within 2–3 years. However, we have inadequate ability to prevent and control their emergences in the first place.

Pandemic prevention should be a global effort on a par with chemical and nuclear weapon prevention. Unless we invest more in critical and creative laboratory, field, and behavioral research, we will soon see additional pandemics of coronavirus and other types of infectious agents not yet imagined (ref.). Understanding how COVID-19 emerged is a critical point on a steep learning curve that we must quickly master. As we face the mounting deaths and societal upheavals of the COVID-19 pandemic, we must not lose sight of how this pandemic began, how and why we missed the warning signs, and what we can do to prevent it from happening again—and again.

References

Identification of the references can be found in the original report and are not necessary for our purposes here.