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Editorial

Another coronavirus, another epidemic, another warning

The world's attention is focused on the 2019 novel coronavirus outbreak, which began in Wuhan China this past December. In the last two decades, this is the 3rd coronavirus that has crossed the species barrier to cause significant human infections. All three (SARS, MERS, COVID-19) are zoonoses, and that understanding is critical to thinking through counter-measures toward identifying, managing, and preventing future outbreaks. Throughout SE Asia, but particularly in China, so-called "wet" markets provide the perfect set of circumstances for the emergence of new viral variants with the potential for human infection. Having visited these markets myself, it is clear how and why these markets facilitate the emergence of these viruses. Domestic and international exotic animal species—including birds, reptiles, fish, and mammalian species—are held in cages sprawled across both large and small markets. The animals themselves are stressed, subjected to inhumane conditions, jammed above, beside, and below cages of other animal species to which they normally would never be exposed. The trade in such animals is unregulated and without regard to the negative impact on either animal or human health. Animals are slaughtered at the market—entrails, carcasses, and meat sit in the open air without ice or refrigeration. In fact, I never witnessed any handwashing facilities, ice, and other normal food handling precautions. In short, this is the perfect "petri dish" environment for the recombination of a variety of viruses that under normal circumstances would never encounter one another. To this is added hundreds of thousands of people, both ill and well, frequenting these markets. It is not by chance that these viruses emerge from such conditions.

The number of cases continues to exponentially increase, with an ever-increasing death toll. To date (February 12, 2020), it appears that the case-fatality rate is on the order of 2%. A significant and critical, and as yet unclear, issue is the R_O (i.e., reproductive number) of this virus. Current estimates are that it is in the 2.5 range, but some modelling suggests it could be as high as 2.68–3.5. This has critical implications in terms of the likelihood of further, large-scale, global spread, and the control measures that will become necessary to decrease the health and economic toll of this virus. This is a rapidly evolving situation that requires transparent cooperation globally, and it is clear we sit on the verge of a pandemic.

So is this just SARS, repeated? Several significant differences from the 2002–2003 SARS outbreak exist. Chief among those are the unprecedented movement of people and animals. Air traffic out of China is estimated at 6-fold higher than during the 2002 SARS outbreak. Such movement leads to millions of people, while asymptomatic or minimally symptomatic, quickly moving across the globe, which increases the rapid, global spread of the virus. Also different is the speed with which the virus was sequenced, identified, and diagnostic assays developed.

What isn't appreciably different is the lack of significant and sustained progress in the development of countermeasures, including antivirals and vaccines to treat and prevent coronavirus infection, respectively. Certainly, much has been learned. Since the 1960s, seven coronaviruses have been identified as causing human infections. Four of those are best adapted for upper airway infection and are responsible for an estimated 20–30% of seasonal upper respiratory infections. SARS, MERS, and COVID-19 are the remaining three coronaviruses that have infected humans. With certainty, more will emerge to cause new human infections, and in time, more lethal viruses are likely to evolve capable of efficient human infection and transmission.

Since the SARS outbreak, research has slowly preceded on both antiviral and vaccine development. Broad-spectrum antivirals (for other purposes, e.g. Ebola, HIV) have been developed and are being tested *in vitro* and in animal models for efficacy against 2019-nCoV. Multiple vaccine approaches including whole inactivated virus, live attenuated virus, mRNA and DNA approaches, recombinant viral protein and nanoparticle approaches have all been devised. Notably, none of these products have progressed past phase I studies over the last 18 years. Significantly, 18 years is just past the public, public health, media and funding agency attention span such that research funding languishes. Development of critical antivirals and vaccines and the scientists who develop them is not a spicket that can be turned on and off at will. One bright spot has been the news that CEPI awarded $11 million in awards to 3 companies with vaccine candidates. Moderna, in partnership with the NIH, likely has the most advanced mRNA candidate vaccine; however, DNA vaccines producing the S protein and viral protein vaccines are also in preclinical studies. The Gates Foundation has also pledged $100 million in funding towards novel coronavirus work.

Another bright spot is that our knowledge of coronavirus receptors, immunology, and vaccine approaches that can be useful in devising vaccines has progressed somewhat. For example, the S protein spike appears to be critical in devising vaccine approaches that lead to the development of neutralizing antibody and blocking of S1-receptor binding. For SARS and COVID-19, the human respiratory epithelial cell receptor appears to be ACE2. Coronavirus infection downregulates ACE2 expression, and this is concerning as ACE2 expression is protective for respiratory epithelial cells. Other studies have suggested that serum neutralizing antibody alone, based on early animal studies, appears to be insufficient and does not provide a mechanism for viral clearance. For this rea-

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son, vaccines that stimulate both neutralizing antibody and T cell immune responses are likely to be the most efficacious—but much remains to be learned in this regard.

Of particular concern, and somewhat reminiscent of the inactivated RSV vaccine story, has been the identification of Th2-type hypersensitivity lung immunopathology after receipt of several different SARS vaccine candidates in small animal models. Such vaccines provided varying levels of protection against subsequent viral challenge but at the cost of inducing other lung pathology. Much more needs to be learned about the mechanism of such reactions.

Many questions must yet be answered as coronavirus vaccines are developed. Research questions whose answers have immediate and practical application include these issues:

- Further resolution of case-fatality rates, viral reproductive number, and serosurveys that allow us to better appreciate the epidemiology of this infection
- The identification and role of possible super-spreaders
- Propensities for differential infection and transmission rates, as well as disease severity and fatality by age and ethnicity
- Development of suitable animal models that closely mimic human pathophysiology and immunology must be identified and better optimized
- Regulatory pathways for vaccine clinical trials and licensure in the absence of continuing outbreaks must be determined, as history demonstrates the intermittent and sudden appearance of outbreaks with these novel viruses—how might such regulatory pathways be altered in the event of a pandemic or more lethal mutations?
- How shall issues of immunosensecence in the elderly and immunoimmaturity in infants and children be accounted for?
- Why have we not seen widespread or lethal infections in children compared to adults?
- What about special populations such as health care providers, pregnant women, immunocompromised individuals, and those with and without prior experience with various types of coronavirus infection?
- How will such vaccines be equitably distributed—particularly in low income countries?
- Better data on viral pathogenesis and human immune responses

As the world waits and watches, it is apparent that Chinese authorities in particular, and all countries, must take more seriously the threat of these emerging coronavirus human pathogens. Specific steps should include the following:

- Regulate so-called wet markets with bans on the unregulated sale and trade in exotic animals.
- Improve sanitation in such markets with food protection and hygienic standards appropriate to 21st century practices.
- Significantly expand public health infrastructure. Among such tasks must be the regular surveillance of these markets for emerging viruses of concern.
- Transparently, quickly, and in accordance with international health regulations, share information with global health authorities. The current outbreak is highly likely to have started in November or earlier, but it was not until late December that Chinese authorities reported to the WHO what was happening.
- Allow, from the very beginning, health authorities from across the globe to assist in outbreak investigation and scientific investigation. It is surprising that CDC has not yet been invited to China to assist in this global issue. It is surprising to see papers from Chinese scientists that place barriers on sharing information—such as requiring "detailed study protocols and statistical and reporting plans" submitted for approval before data is shared. This is counter to the essence of professionalism and moral imperatives to openly share science for the protection of the health of the global public.

MERS had an estimated 35% case-fatality rate, SARS 10%, and nCoV an early estimated 2–3% CFR. These are pathogens of great concern to all humans in all countries. It is imperative that science proceed unimpeded by politics and health authorities seeking to place the most positive "spin" on a global health crisis. All countries must invest, in a sustained and serious manner, in preparedness and other countermeasures. The world needs a coordinated, intentional, and explicit "playbook" with coordinated country and global plans for dealing with each category of pathogen capable of causing epidemics and pandemics. Waiting until it happens, and then trying to devise plans as an epidemic or pandemic proceeds is "too little, too late." As a service to our readers, we have put together a Coronavirus Resource Center (https://www.elsevier.com/connect/coronavirus-information-center) where we will collate important papers and policies as we are aware of them.

This outbreak demonstrates once again that, even in the second decade of the 21st century and in the context of a country with a huge economy, "preparing, identifying, and sharing" is a far better, cheaper, and more successful strategy than "wait and play catch-up after the fact." We are once again building the airplane while we are flying it—particularly outside of developed Western countries. Perhaps Albert Camus said it best: "They fancied themselves free, and no one will ever be free so long as there are pestilences."

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