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The spread of the COVID-19 coronavirus

Health agencies worldwide prepare for the seemingly inevitability of the COVID-19 coronavirus becoming endemic

Philip Hunter

While air travel from and to China has subsided and cases of people infected with the COVID-19 coronavirus appear all over the world, virologists, epidemiologists and public health experts are worrying that the virus could eventually become endemic in the human population as it has already spread beyond the Wuhan region where the Chinese government has enforced a strict quarantine. To no avail though as new outbreaks occurred in Japan, Korea and Northern Italy, along with patients being hospitalized in Austria, Germany, New Zealand and other countries at the time of writing. While it seems too late to contain the virus in the Wuhan region, the outbreak has enormously spurred research on the virus itself, along with a better understanding of its pathogenicity and vaccine development.

A lesson from SARS

The 2002 SARS outbreak in southern China has only limited value for predictions, even if both are coronaviruses. SARS largely died out during the Northern Hemisphere summer of 2003 when the virus became significantly less infectious. However, while the COVID-19 virus appears to be considerably less lethal than SARS, which had a fatality rate of 9.6%, killing 774 of the 8,098 reported patients [1], it is more infectious. And though the virus was very quickly identified and its genome sequenced, it does not automatically translate into detailed information about infectivity, virulence and how it interacts with the human immune system.

One of the earlier suggestions that has now been largely scotched was that the COVID-19 virus became infectious before patients showed the first symptoms, which would make containment measures such as quarantining less effective, like locking the stable door after the horse has bolted. This hypothesis arose after a cluster of cases was reported in Germany, appearing to have originated from an individual who had flown in from China but did not report symptoms until after returning to China. However, as was pointed out by Amesh Adalja, Senior Scholar at the Johns Hopkins Centre for Health Security, it was then established that the person had indeed experienced symptoms in Germany before they were reported by other people in that cluster.

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What is true though is that a significant number of people infected have experienced mild symptoms, which itself is a problem during the early stages of an outbreak when strenuous efforts are being made to prevent its spread. It means some cases will go undetected because the symptoms are so mild that coronavirus infection is not suspected, at least initially. As Jeremy Farrar, Director of the Wellcome Trust, pointed out early on, the wide range of severity in symptoms is one of the major challenges: the cases of patients with only very mild symptoms, or people who are asymptomatic, may be masking the true numbers infected and the extent of person-to-person transmission.

Several key aspects of the COVID-19 virus are more clear now, one being that it is likely to subside during the summer similar to the SARS outbreak in 2002 as most coronaviruses become far less infectious under warm weather. "These respiratory infections all tend to be winter diseases", said by Paul Hunter, Professor of Health Protection at the Norwich School of Medicine, University of East Anglia, UK. "The big one that stopped SARS was summer in the Northern Hemisphere". This has the corollary that warm countries are much less affected; Hunter noted there was only one single case of SARS in the whole of Africa and that was South Africa where there are seasonal variations in temperature. However, he also cautioned against complacency, noting that Mexico experienced quite a high number of cases during the 2009 influenza A H1N1 pandemic, despite the country being hot except at higher altitudes inland. "So there are other factors determining infectivity beyond temperature", Hunter added.

Infectivity versus mortality

It is, however, the virus' infectivity which has prompted fears that it could become endemic. "It is substantially less lethal than SARS but a lot more infectious", Hunter said. "On the other hand, it is substantially less infectious than seasonal influenza, but more lethal". As a result, the degree of severity has been exaggerated by the data so far: while almost all the extreme and fatal cases have been notified, there has been considerable underreporting of mild cases. Early data on closed cases, that is people who had either died or recovered, indicated a fatality rate as high as 20%. At time of writing, however, the death rate among more recent cases had subsided to about 1.5% with the highest risk for the elderly.

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This pattern is typical of most respiratory virus outbreaks, even if part of the effect is an illusion resulting from the fact that reporting of less severe cases only tends to catch up later on. It also reflects the common decline of virulence during such epidemics, partly resulting from strong selective pressure imposed by social distancing, quarantine and other public health measures [2]. These measures reduce the rate of transmission and slow down progression of the outbreak, giving the virus more time to attenuate. Social distancing amplifies selection for longer-surviving low-virulence sub-groups, so that the majority of the population during the later stages of an outbreak are exposed to less virulent phenotypes [2].

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In addition, many of the most vulnerable individuals are infected earlier on, so that later cases are also less serious because they involve more robust individuals, according to Hunter. "In the longer term, the Wuhan virus should not be anywhere near as serious, because an endemic disease affects more young people who are by then the 'non-immunes'", he said. That was indeed the case even for the great Spanish Influenza Pandemic 1918/19, which caused a much larger proportion of severe cases and deaths among younger people than most other flu outbreaks. "That was when Spanish flu was in its first flush, not after it had become endemic", Hunter explained.

A prompt response

Seen in this light, criticisms of the quarantining and other social distancing methods employed against the coronavirus are either overreactions or wide of the mark. Even if they fail to contain the outbreak, they effectively accelerate the attenuation process and should reduce the number of severe cases and fatalities. In this regard, the Chinese authorities have won widespread praise for the rapid reactions once the severity of the outbreak had become clear, both in terms of identifying the virus and of isolating infected individuals.

"The excellence of the Chinese response is first of all making the early diagnosis that it was coronavirus and secondly that it was a novel coronavirus, and then sequencing the genome in very short order was brilliant", said William Schaffner, infectious diseases specialist at Vanderbilt University Medical Centre, Nashville, Tennessee, USA. "Then they did something else that was also terrific, that they had learnt from SARS. They communicated that information transparently, completely, honestly and instantaneously to the world's scientific community. That meant three things happens immediately. Firstly countries around the world, including our own CDC (Centres for Disease Control), quickly ran their own PCR tests in their own laboratories and so were able to implement testing very promptly. Number two, within hours of transmission of that genomic information, people began working on a vaccine. [...] Number three, research began looking for therapies, both new compounds and among existing compounds that might have an effect on that virus".

Schaffner, also a past president of the US National Foundation for Infectious Diseases, was less complementary though about the Chinese communication about transmission within the key areas, especially Wuhan. "Over time on the public health side we have established very standard methods pioneered by the CDC epidemiologists to do public health interventions in the field", he explained. "There is concern that those rigorous epidemiological methods still have not been employed optimally in China. That public health information and the clinical information is only just now being shared. There has been reluctance on that aspect to transmit that information transparently and quickly." As Schaffner added, the WHO and CDC now have standing offers to work with their Chinese counterparts in the field but so far those have not been accepted.

According to Schaffner, the Chinese command and control method of governance has enabled them rapidly to quarantine up to 50 million people in the affected areas, but it works less well when it comes to disseminating more sensitive information. He does feel it is a missed opportunity for China to show itself in a positive light. "I think it ought to have been a matter of national pride", said Schaffner. "It should have been an opportunity to show how open the country is to the world".

"Social distancing amplifies selection for longer-surviving low-virulence sub-groups..."

This could also delay the return to normality when the outbreak does start subsiding. Schaffner identified two possible metrics that could be used by global health authorities to determine when it would be safe to return to business as usual. "One is a determination of new cases in Wuhan", he explained. "But to have confidence in that metric we need to be sure that testing intensity is reasonably constant. [...] We are not sure how reliable that is." Schaffner therefore suggested that the rest of the world would be unable to rely on that metric. "There may though be one other metric that can help us and that is the number of exportations from Wuhan and Hubei (the other area district at the epicentre of the outbreak) to other parts of China and the rest of the world", he added. "If you can show a diminution in those exportations that will give public health and governments generally the confidence they can back off some of these quarantine restrictions".

Vaccines and other therapies

There is though growing optimism over developing therapies against the COVID-19 virus. This applies particularly to vaccines and antibodies to neutralize the active sites of the virus surface that expedite the penetration of host cells, according to Michael Farzan, Co-chair of the Department of Immunology and Microbiology, Scripps Research, La Jolla, CA, USA. "This virus is a close cousin of SARS-CoV, and like SARS-CoV, it 'chooses', meaning has been selected, to move rapidly from host to host before an adaptive immune response emerges", he explained. "Because of this, and unlike HIV-1 and Ebolavirus, it keeps its key epitopes exposed, probably so that it can be more efficient at binding the next cell. This makes it very vulnerable to antibody neutralization, and thus it is a relatively easy virus to protect against. I refer to it as 'stupid' on a spectrum where HIV, which lives in the face of an active immune system for years, is a 'genius'".

Furthermore, as Farzan added, it does not mutate rapidly for an RNA virus

because, unusually for this category, it has a proof-reading function in its polymerase [3]. "In short, a vaccine, and especially a vaccine targeted in part to the receptor-binding domain of the 2019-nCoV entry protein, the Spike or S protein, should be effective", he said. As this protein is protected against mutation, a vaccine would not need regular updates, unlike seasonal influenza vaccines.

Secondary infections

Another longstanding question is the exact sequence of events and interactions with the host immune system in severe and fatal cases. Death usually results from respiratory failure following pneumonia, which is either caused directly by the virus or caused by secondary infection by opportunistic bacteria, such as *Streptococcus*. In the case of influenza outbreaks, pneumonia usually results from secondary bacterial infections that come in only when the primary virus infection has subsided. Indeed, the majority of deaths associated with the great Spanish Influenza pandemic of 1918–1919 were caused not by the influenza virus alone, but by bacterial pneumonia following the initial viral infection [4].

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Unlike influenza viruses, however, some coronaviruses such as COVID-19 are believed to cause pneumonia directly, although that does not prevent subsequent bacterial secondary infections. There is already evidence that the virus has caused some severe cases of pneumonia directly, with no evidence of other known respiratory viral or bacterial pathogens after conducting microbiological testing [5].

There is still debate over the relative roles of primary viral and secondary bacterial pneumonia in the Wuhan outbreak and how to deal with it. Hunter is convinced that it is a primary viral pneumonia, echoing some of the early studies as well as more extensive analysis of the SARS outbreak [6]. "My reason for that is people are saying antibiotics don't work in this case and they work for secondary pneumonia but not primary. Also, the early symptoms of this novel coronavirus infection are in the lower respiratory tract". This again is unlike most if not all influenza virus strains, where lower respiratory tract symptoms come later, presumably from secondary bacterial infection.

Hunter agreed though that some patients will get secondary bacterial pneumonia as well and that could account for some of the severe cases. However, John Edmunds, who develops control programmes for disease at the London School of Health and Tropical Medicine in the UK, reckons that the relative roles of bacterial and viral pneumonia are not yet clear. "Some anecdotal reports seem to suggest that most patients are initially OK, and then get severe disease, which might indicate a bacterial superinfection, but how consistent this pattern is is anyone's guess. Again, there is a lack of clinical as well as epidemiological data that are coming out", Edmunds commented. This question of viral versus bacterial pneumonia is important for treatment, because the latter would require the routine use of antibiotics, whereas the primary viral infections would be treated with anti-virals and antibodies.

Overall, as the outbreak continues to develop and new data come out of China, there are at least good prospects of treating patients with anti-viral and antibody treatments until an efficient vaccine becomes available.

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