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COVID UNANSWERED QUESTIONS

How are covid-19 symptoms changing?

With new variants and a changing landscape of vaccination and immunity, what do the symptoms of covid-19—and our understanding of them—now look like? **Mun-Keat Looi** reports

Mun-Keat Looi *international features editor*

How have covid symptoms changed since the start of the pandemic?

In the short space of a few years we've seen surprising changes in the way covid-19 presents. At the start of the pandemic the first commonly reported symptoms were loss of smell and taste, followed by shortness of breath and a cough, followed by vascular injuries, says David Strain, senior clinical lecturer at the University of Exeter Medical School. "That became the standard that we expected," he says.

Betty Raman, senior clinical research fellow in the Radcliffe Department of Medicine, University of Oxford, says, "People presenting with the earlier variants would have quite severe cardiorespiratory or mostly respiratory symptoms in the acute phase with other symptoms too, like brain fog. Quite a significant proportion were admitted to hospital with the earlier variants."

Since then there's been an evolution of symptom clusters and manifestations across the variants, she says, affected by the evolution of the virus itself but also by vaccines, the vaccine landscape, the use of other treatments, and people getting recurrent infections. This has led to falling hospital admissions and changes in the frequency of each symptom.

Strain says that the loss of sense of smell and taste is nowhere near as prevalent as it used to be. "That really happened at the time of omicron," he says. "Omicron subvariants BA.1 and BA.2 seemed to migrate from [infecting mainly] lungs and nervous tissue to the upper airways. BA.1 for many people was little more than a severe head cold."

Raman adds that, while some people still experience brain fog, on a population scale this seems slightly less prevalent with newer variants and vaccines.

Strain estimates that at the start of the pandemic infection resulted in vascular damage in around 15-20% of patients—"for some this was simple 'covid toes,' but for others it was pulmonary emboli and acute kidney injury"—while a smaller proportion went on to experience a full cytokine storm and acute respiratory distress syndrome (ARDS). "Thankfully, ARDS has almost completely disappeared now that we've got vaccination," he says. "Very, very few people get onto that final stage."

With vaccination, immunity from prior infection, and the evolution of omicron to cause overall less intense acute infection, the presentation of symptoms has evolved. Strain says that we now see mostly upper respiratory symptoms, fever, myalgia, fatigue,

sneezing, sore throat, and cough. He notes that many of these are not specific to covid-19 and could also be a manifestation of other viral illnesses.

World Health Organization list of covid-19 symptoms

Common

- Fever
- Cough
- Tiredness
- Loss of taste or smell

Less common

- Sore throat
- Headache
- Aches and pains
- Diarrhoea
- Rash on skin or discoloration of fingers or toes
- Red or irritated eyes

Most serious

- Chest pains
- Confusion
- Loss of speech or mobility
- Difficulty breathing¹

Are particular symptoms associated with particular variants?

When the alpha variant arrived, a small study in Italy reported that it was associated with greater risk of muscle pain, insomnia, brain fog, anxiety, and depression,² while data from the ZOE symptom tracker app indicated that runny noses had become more common during the delta wave.³

Data from ZOE indicate that subvariants BA.4 and BA.5 are more likely to cause sore throats and a hoarse voice.⁴ Tim Spector, lead investigator at ZOE, has said that fatigue in the morning, even after a good night's sleep, and a sore throat could now be considered to be signs of infection.⁵ Night sweats and insomnia are also symptoms that have cropped up more commonly in the recent BA.5 era.

Strain says that with the BA.2 subvariant the vascular component meant that a key symptom most people presented with was fatigue, not getting enough sleep, or "non-restorative sleep—basically, they would be waking up and feeling exhausted as if they hadn't rested, as if they hadn't slept at all."

The BA.1 era also saw a rise in children presenting with symptoms, Strain adds. "[Our hospital] went

through the whole of the wild-type, alpha, and delta waves with no more than one or two children ever in hospital with it,” he says. “And then we hit BA.1, and we suddenly had 10 or 12 children in hospital with the croup, the whooping cough that it was causing.”

But in retrospect, he says, this was purely because children’s upper airways are smaller, so they were more affected by the aforementioned shift in viral behaviour with omicron. “In adults it was very, very minor,” he says, and “didn’t cause problems.”

More worrying is that delirium—a constant symptom throughout the pandemic, particularly in elderly people who are most vulnerable to covid-19—is also taking longer to resolve now, says Strain. “With BA.1, older adults who got covid would get a delirium for about 2-3 days, but it would resolve,” he says. “With BA.4 and 5 it’s taking weeks to get better—we’re back to getting people to go to community hospitals or short term care homes while we wait for delirium to resolve.

“The knock-on effect is the pressure on hospitals: at least one of our geriatric wards has got nothing but covid delirium in. They’re no longer infectious, they don’t need to be there, but they are people who are not safe to go home.”

A study published in *Lancet Psychiatry* last August noted that more neurological and psychiatric disorders were seen with the delta variant than with the alpha variant—and that omicron was associated with similar neurological and psychiatric risks.⁶

Raman cites a study using data from the ZOE app that examined various long covid clusters based on variants. “What is quite notable is that the neurological symptoms after acute covid-19 do appear to be quite a dominant feature in patients with the older variants: the wild-type, alpha, and delta variants,” she says. “What is clear is that the neurological symptoms, including brain response, were definitely a feature, quite a prominent feature of the older variants. And there are increasing numbers of reports that it’s becoming less.”

What we don’t know, adds Raman, is whether this is due to vaccination and immunity. She says, “Our immune system is now better equipped to fight [covid] infection. And therefore, that overwhelming response that we used to see in the early phase of the pandemic is no longer present and may not be contributing to some of the more severe manifestations that we were seeing at the start of the pandemic.”

What makes symptoms more severe?

Vaccine status, viral load, underlying medical conditions, and autoimmune disease can affect the severity of the symptoms, says Monica Verduzco-Gutierrez, professor and chair of the Department of Rehabilitation Medicine at the Long School of Medicine in Texas. Each individual’s immune response will vary. She adds, “Of course, now we have therapeutics that can be started at the onset of symptoms. Access to those therapeutics will affect the severity of the symptoms.”

Raman says that people with comorbidities such as obesity, diabetes, or heart disease tend to have a lower reserve from a physiology perspective. She explains, “They have lower physiological reserve to deal with infections—not just coronavirus infections but other infections as well. And it’s not just the body’s capacity to deal with the increased oxygen demand, the increased demand for nutrition and energy, but also the immune [cells] reserve ready to fight and clear the infection. Even that seems to be lower in patients with multiple comorbidities.”

She adds, “A lot of these conditions are inflammatory themselves. So, you have an immune system that is constantly activated because

of damage being done, either as a result of the disease or as a cause of the disease. That essentially keeps the immune system constantly working . . . there’s exhaustion of the immune system, which then becomes maladaptive or is dysregulated. And that contributes to a response that lasts longer, that may be more severe, maybe even associated with cytokine storm.

“It’s a dysregulated immune system which seems to be important and critical in determining severity of acute infections.”

How might symptoms change in the future?

Strain suspects that one of the BA.4 and BA.5 variants “is definitely causing the respiratory illness again . . . We are starting to see covid pneumonia reappear, although it’s nowhere near as severe as it was in the first instance.”

That said, he adds, “I don’t think anyone is expecting it to head back to the lungs. From an evolutionary point of view, the jump to the airways has made it far more transmissible because you can start spreading it sooner. You need lower concentrations of it to become infectious because you are right in the upper airways rather than deep in the lungs. Just breathing and talking is spreading.”

But he warns that this doesn’t mean that it won’t become more serious in different ways. “The big fear is the disease moving to a more thrombogenic approach,” he says. “We saw that with BA.2. We saw it with the delta variant—that we were getting massive D-dimer rises [indicating] massive clot risk.”

Previous variants have seen more covid patients presenting as much as 12 months later with heart attacks or strokes, and there’s an increased risk of type 1 diabetes and possibly of dementia. Only time will tell if this was a feature of the earlier variants and whether it will persist with omicron.

Do you have a “Covid Unanswered Question”? Email mlooi@bmj.com, and we’ll try to cover it in a future instalment of this series.

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