Why calculating the risk of the AstraZeneca vaccine is so difficult

April 22 2021, by Jj Coughlan

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Both the European Medicines Agency and the UK's Medicines and Healthcare products Regulatory Agency have concluded there's a possible link between the AstraZeneca vaccine and rare forms of blood

clotting. However, the responses of different countries to these findings have varied significantly.

Denmark has withdrawn the vaccine entirely. In Germany the vaccine is only being given to over-60s, while France has decided that under-55s should get different COVID vaccine for their second dose. But in the UK, authorities haven't mandated any action, saying only that it would be preferential to offer under-30s an alternative vaccine where possible.

These are significantly different positions, so how can we make sense of them? How risky is the vaccine? Unfortunately, reaching a definite conclusion is difficult, and this perhaps explains some of this variation between countries. Here's why it's so challenging.

Calculating risk

Two specific clotting disorders have been linked to the AstraZeneca vaccine: cerebral venous sinus thrombosis (CVST), where clots form in the veins that drain blood from the brain, and splanchnic vein thrombosis (SVT), where clots form in the abdominal veins. They've coincided with people having low platelet counts (thrombocytopenia), with CVST appearing more frequently.

To determine the risk posed by the vaccine, the key question is: are a higher percentage of people developing these rare clots after receiving the vaccine than would do so normally? Here's what's known so far.

As of April 4, 34 million AstraZeneca doses had been given in Europe, with 169 CVST and 53 SVT cases reported. In the UK up to the end of March, 20 million doses had been given, with 54 CVST and 25 SVT cases. Put together, this equals around one case of CVST per 240,000 doses and one of SVT per 690,000 doses.

A commonly quoted estimate for the background incidence of CVST is around one case per 200,000 people per year. Given the rate of CVST post-vaccination is higher than this, and rollout has only been going a couple of months, this does suggest a raised risk of clotting.

To put this in context, if every person in, say, Ireland (population 5 million) was to receive the vaccine, we might expect around 21 cases of CVST to occur. These would probably be on top of the 25 cases we'd expect to occur each year anyway, without vaccination. So the overall risk is very small.

However, there are major limitations to comparing estimates like this.

First, CVST occurring post-vaccination appears to coincide specifically with a low platelet count. This is a novel phenomenon and has been given a specific name: vaccine-induced immune thrombotic thrombocytopenia. Usually, CVST isn't associated with immune-driven thrombocytopenia. As a result, it might not be appropriate to compare CVST that follows vaccination with that which happens otherwise—they could be quite different conditions.

Also, CVST is rare, which makes background estimates intrinsically uncertain. Although the background rate above is referred to a lot, others exist, and some are considerably higher. The incidence of CVST can also vary with age, sex and other risk factors. For example, the oral contraceptive pill has been associated with a sevenfold increase in the risk of CVST in women aged 15-50.

This may be particularly relevant because the AstraZeneca vaccine has been disproportionately given to younger female populations in some countries. In Germany, for instance, the vaccine was offered to medical staff and teachers, who tend to be female. Part of the CVST risk observed with the vaccine might be due to a greater underlying risk in

those receiving it.

Another potential issue is that COVID-19 itself has also been linked to increased risks of both clotting and low platelets (indeed early research, awaiting review by other scientists, suggests the risk of getting CVST after COVID-19 could be eight to ten times what it is after vaccination). So the pandemic may be increasing the baseline risk for these rare blood clots too.

It's also possible that the vaccine might trigger CVST in patients who have an underlying predisposition to developing the condition, meaning that some cases arise after vaccination in patients who would have developed the condition anyway. All these factors make assessments of the vaccine's risk uncertain.

So what to do?

In the meantime, a pragmatic approach could be to compare the potential risk of these rare clots with the risk posed by COVID-19.

All the approved vaccines, including the AstraZeneca vaccine, provide excellent protection from severe and fatal COVID-19. The risk of severe COVID-19 is lower in the young, and also falls for everyone when the amount of virus circulating in the population is lower. Yet despite this, the UK government calculates that the risk-benefit ratio still favors taking the AstraZeneca vaccine in almost all cases. Only when the risk of exposure to the virus is low does it become beneficial for under-30s not to take it.

It's worth remembering, too, that among the young, COVID-19 can still kill. In the UK, it's estimated that one in every 2,500 people aged 25-44 who get COVID-19 will die—which is 400 times the fatality rate attributed to vaccine-related blood clots in Britain. If you're at greater

risk of catching the virus, perhaps because of your job, then taking the vaccine makes sense.

Note, too, that other COVID-19 vaccines may also carry risks, which might emerge only after wider use. For example, anaphylaxis has been reported after one in every 90,000 Pfizer vaccine doses, and the Johnson & Johnson vaccine may also cause blood clots.

If the link between clotting events and these vaccines is confirmed, and this risk is shown to be primarily in specific groups, then the use of alternatives in at-risk groups would be appropriate. In the meantime, remember that no decision is risk free, and that not taking a COVID-19 vaccine also represents a risk.

Provided by The Conversation