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VACCINATION

Covid-19: How AstraZeneca lost the vaccine PR war

AstraZeneca's covid-19 vaccine has rarely been out of the news—and the headlines show no signs of abating. Jacqui Wise explains how miscommunication and politics created a nightmare for the company and the global vaccination effort

Jacqui Wise *freelance journalist*

Hailed as a "vaccine for the world" with its low price and easy storage requirements, AstraZeneca's vaccine candidate has faced a string of setbacks in 2021 with questions over effectiveness, possible side effects, and long running disputes about supplies.

It's not clear why the Anglo-Swedish company and its vaccine have been singled out for so much criticism, but poor communication seems to be at the heart of the problem. Martin McKee, professor of European public health at the London School of Hygiene & Tropical Medicine, says, "This is a company that has taken an innovative product to market in record time but has mishandled communications at every step. Trust and confidence are so important for vaccines—you can't divorce the two."

Clots

AstraZeneca's latest crisis is possibly also its biggest so far. Its vaccine has been linked to thrombosis, as well as a rare type of blood clot in the brain called cerebral venous sinus thrombosis (CVST), with a number of episodes in younger women.

The vaccine was authorised for use in Europe at the end of January and started to be used more widely in February. On 7 March Austrian authorities announced that they were investigating a death that was possibly vaccine related. A few days later Denmark and Norway were investigating reports of blood clots and a death after vaccination. On 15 March Germany suspended its use of the vaccine, followed swiftly by several other countries.[1 2]

The European Medicines Agency (EMA) and the World Health Organization say that the vaccine's benefits outweigh any risks: the EMA undertook an in-depth review of the issue and, while acknowledging a "possible" link to blood clots that should be listed as "very rare" side effects, on 7 April it confirmed that the "overall benefit-risk remains positive" for the vaccine's continued use.[3] The cause of the clots is still unknown, with research ongoing.

In the UK, which has ordered 100 million doses of AstraZeneca vaccine, the Joint Committee on Vaccination and Immunisation (JCVI) advised on 7 April that people aged under 30 should be offered alternative vaccines where available—even though the Medicines and Healthcare Products Regulatory Agency (MHRA), which conducted the UK review of the evidence, emphasised that it was "not recommending new age restrictions in COVID-19 Vaccine AstraZeneca vaccine use."

The MHRA said that, up to 31 March, 79 thrombosis events with low platelets had been reported from over 20 million doses of the vaccine administered. Among these reported cases, 19 people have died. The overall risk of these blood clots is about four people in every million who receive the vaccine.[4]

At the time of writing, Australia, Belgium, and France had restricted the vaccine to people aged over 55, while Italy and Spain limited its use to over 60s after the EMA's announcement. Scandinavian countries had already paused their rollouts of the vaccine, while Canadian provinces had suspended its use in under 55s on 30 March. Several German states have also suspended its use in under 60s.[5]

Ines Hassan, senior policy researcher with the Global Health Governance Programme at the University of Edinburgh, sees a positive in the way the issue is being investigated. She says, "The scrutiny from regulators and pharmacovigilance experts shows that the system and safety monitoring procedures are working as they should."

What's not helpful is how it's been communicated. Whether from different regulators, government officials, academics, or the media, Hassan tells *The BMJ*, "It is clear that the mixed messaging from these different stakeholders has caused confusion among the general public, and it has already led to increased vaccine hesitancy in some parts of Europe among other regions."

Martin McKee says that, although the MHRA and the JCVI have different roles, it's "extremely regrettable" that one is advising no age restrictions while the other proposes that people under 30 should be offered an alternative. Those aged from 30 to, for example, 50 will wonder why the UK guidance, even if contradictory, differs from that in other countries. He adds, " I have previously criticised messaging about the AstraZeneca vaccine. Sadly, it seems that we have learnt little."

In the US

Adding salt to the wound, AstraZeneca had simultaneously but separately faced criticism in the United States. In a 22 March press release the company announced the long awaited results of a key US trial, one that it hoped would finally win emergency use approval for the vaccine from the US Food and Drug Administration. The FDA has been

cautious around the AstraZeneca vaccine: it has yet to issue approval for its use in the US despite approving vaccines from Pfizer, Moderna, and Johnson and Johnson (Janssen) and nearly four months since the UK approved it.

In the March announcement AstraZeneca said that the results showed a 79% efficacy in preventing symptomatic disease.[6] Hours later, however, the US National Institutes of Health (NIH) took the unusual step of issuing a midnight statement saying that its Data and Safety Monitoring Board had "expressed concern that AstraZeneca may have included outdated information from that trial, which may have provided an incomplete view of the efficacy data."[7]

AstraZeneca says that the agreed cut-off point for data was 17 February, as publicised in its initial release. In response to the NIH, within 48 hours it added more recent data and revised the efficacy down to 76%. The US chief medical adviser, Anthony Fauci, called this an "unforced error" on AstraZeneca's part. Speaking on *Good Morning America*, he said, "It was not necessary—if you look at it, the data really are quite good, but when they put it into the press release it wasn't completely accurate."

McKee says that it is "completely unprecedented that a data monitoring committee would say that what you said in a press release was not accurate. It's so basic that you don't issue contradictory information. What on earth was going on there that they didn't check?"

However, Peter English, a retired consultant in communicable disease control who is former editor of *Vaccines in Practice* magazine and immediate past chair of the BMA's Public Health Medicine Committee, has sympathy for the company. "It seems like it was an attack on the company and not founded on science," he says. "AstraZeneca had stated in advance in their protocol the time period, so [they] couldn't cherry pick the data. If they had done it other way round they would rightly have been criticised."

He tells *The BMJ*, "It was incredibly irresponsible of the NIH [to issue that statement], as it implied there was something terrible going on—which we found out a few days later wasn't the case. It brought the vaccine into disrepute based on nothing. This harms confidence in all covid vaccines and in vaccines overall."

Early troubles

Part of the problem may be that AstraZeneca isn't a traditional vaccine manufacturer. McKee tells *The BMJ*, "A number of commentators have raised questions about the experience of the board in communicating some of the challenging messages around vaccines."

Oxford University, which developed the vaccine, originally intended to partner with the US company Merck, but the UK government—which had invested £65.5m (€75.7m; $90.1m) in the vaccine's development—insisted on a UK based company. (GlaxoSmithKline reportedly turned down a partnership, as it had its own candidates in development.)

Andrew Pollard, the Oxford vaccine group's chief scientist, was delighted that the Anglo-Swedish company agreed to undertake the drug's production at cost and at volume, making it "a vaccine for the world." But it seems that no good deed goes unpunished, and AstraZeneca's learning curve has been steep.

In September 2020, phase III clinical trials of the covid-19 vaccine in Brazil, South Africa, the UK, and the US were temporarily paused because of unexplained neurological symptoms in one of the volunteers.[8] After investigating the incident the MHRA gave the go-ahead to restart UK trials within days, but the FDA maintained the US suspension for six weeks, apparently unhappy that it hadn't been told of the problem quickly enough. This seems to have sparked the general caution in the FDA's approach to evaluation.

Then, on 23 November, AstraZeneca was criticised for the way it announced the vaccine's efficacy. It had combined the results of different trials and had, critics said, missed out key details. Rather than coming up with a single figure for efficacy like other vaccine manufacturers—Pfizer and Moderna had just a week earlier announced higher than expected efficacies of 91% and 95%, respectively—AstraZeneca announced an overall 62% efficacy and another of 90% in people who had originally received a half dose (this followed a dosing error in one arm of the phase III trial, which fortuitously led to better results).[9] The higher number was later reinterpreted as due to a longer gap between doses.

Media reports criticised how AstraZeneca had communicated the information about its trials. "There have been contradictions between statements given to investors, press releases, and internal documents," says McKee. A scientific paper can't be sent out for peer review if it has market sensitive information such that a reviewer or editor could potentially exploit the market position. Preprint publications can face delays, which make it difficult to coordinate with market communications. McKee says that this may be why AstraZeneca relied on press releases—"but, that said, they should be consistent [with their information], and they haven't always been so."

Nevertheless, on 30 December 2020 the UK and Argentina became the first countries in the world to approve the AstraZeneca shot. The year ended with the company marking its first success in the vaccine field but with the shine somewhat taken off. And there was more to come.

Annus horribilis?

On 25 January 2021 the German newspaper *Handelsblatt* claimed that the vaccine had only 8% efficacy in over 65s.[10] The report turned out to be baseless—but not before damage had been done to public confidence in the vaccine across the continent.

A few days later the EMA approved the AstraZeneca vaccine for all age groups in the EU, but that same day the French president, Emmanuel Macron, claimed that it was "quasi-ineffective" for over 65s. After Macron's comments Germany and France initially prevented the drug's use in over 65s. Confusion over which age groups should have the vaccine has contributed, unsurprisingly, to a lack of confidence. More than half of people surveyed in France, Germany, and Spain thought that the shot was unsafe in a YouGov poll published on 22 March.[11]

The timing couldn't have been worse. It came just as AstraZeneca faced a political crisis with the EU around missing vaccine deliveries. The company had agreed to deliver as many as 120 million doses to the EU by the end of March 2021, but yield problems and other issues prompted it to tell the EU that it could supply only 30 million doses (subsequently increased to 40 million). The EU, in the grip of a rising third wave of infections, did not take this well.

Although other vaccines have also had supply problems, AstraZeneca seems to have become a political football between the EU and the recently Brexit-ed UK. The European Commission's president, Ursula von der Leyen, threatened to block AstraZeneca from exporting doses of vaccine to the UK, and the Belgian MEP Philippe Lamberts accused the company of dishonesty and arrogance, saying that it had "over-promised and under-delivered."

At the time of writing the dispute is ongoing, alongside the new blood clot issue.

To cap it all, AstraZeneca suffered another blow in February when South Africa—grappling with rising infections and a worrying new variant of the virus accounting for 90% of the cases in the country—halted the rollout of the AstraZeneca vaccine after a study showed disappointing results against the 501 variant.[12] With countries now looking over their shoulders at new variants and the effectiveness of existing vaccines against them, the decision was another disappointment for the company.

Fallen heroes

Kate Bingham, former head of the UK's Vaccine Taskforce, calls AstraZeneca "heroes" for the way the company picked up the vaccine and worked out how to test, manufacture, and distribute it at low cost around the world. Speaking to the *Financial Times*, she said that the company had become caught up in geopolitics.[13]

Ines Hassan emphasises that AstraZeneca has not fallen short on meeting regulatory requirements: it submitted the necessary data as expected, including when it recently submitted interim analysis findings to the FDA. However, communication about trial design early in development, and later about the number of patients with covid-19 symptoms from its primary analysis, could perhaps have been handled better, she says.

"One big lesson is that transparency is essential, especially with regulators and the general public," says Hassan, while acknowledging that overcommunicating without causing unnecessary alarm is a tricky balance to strike. She adds that the responsibility to communicate safety issues is not the manufacturer's alone—it's the responsibility of regulators, policy makers, public health academics, and the media, among others.

Peter English questions why the one vaccine being sold at cost price is the one that's been the most vilified. "The amount of bad press they have got is not based on the science," he says. "It seems completely disproportionate or unfounded. It looks like a lot of them are attacks on AstraZeneca itself and seem to have an ulterior motive. It almost feels like there is a deliberate misinformation campaign."

But the consequences of AstraZeneca's problems go far beyond one company's reputation and profits. Its vaccine is an indispensable part of WHO's plan to roll out two billion doses to 92 nations by the end of 2021, through the Covax initiative. The UK's order of 100 million doses places AstraZeneca at the heart of its vaccination programme.

And many commentators worry that crumbling confidence in AstraZeneca's vaccine may spill over to others, as the world is already grappling with vaccine hesitancy as an obstacle to wider coverage and an end to the pandemic. As McKee says, "When you lose trust it's really difficult to regain it."

AstraZeneca's six month nightmare

2020

9 Sep Phase III trials are paused after a single event of unexplained illness

30 Dec Argentina and UK approve AstraZeneca vaccine for emergency use

2021

25 Jan German newspaper *Handelsblatt* claims that the vaccine has only 8% efficacy in elderly people

29 Jan European Medicines Agency (EMA) approves AstraZeneca vaccine. President Macron of France claims that it is "quasi-ineffective" in over 65s

9 Feb South Africa halts rollout of AstraZeneca vaccine after study shows disappointing results against the 501 variant

7 Mar Austrian authorities announce investigation of a potentially vaccine related death

10 Mar EMA press release suggests no specific issue with batch used in Austria

15 Mar Germany suspends use of AstraZeneca vaccine, pending investigation of three deaths and four other incidents

18 Mar EMA says that benefits still outweigh risks

22 Mar AstraZeneca announces US trial results claiming 79% efficacy

23 Mar US National Institutes of Health's Data and Safety Monitoring Board expresses concern that AstraZeneca may have included outdated information from the trial. AstraZeneca issues new data and revises the figure to 76% on 25 March

30 Mar Canada suspends use of AstraZeneca vaccine in under 55s

31 Mar German states suspend use of AstraZeneca vaccine in under 60s

6 Apr UK Medicines and Healthcare Products Regulatory Agency (MHRA) pauses a trial of the vaccine in children and teenagers pending investigation of the blood clot link. Marco Cavaleri, EMA head of vaccines, tells an Italian newspaper that "it is clear there is a link with the vaccine [and blood clots] . . . but we still do not know what causes this reaction." EMA distances itself from the comments

7 Apr EMA investigation concludes that "unusual blood clots with low blood platelets should be listed as very rare side effects" for the vaccine but that "overall benefits of the vaccine in preventing covid-19 outweigh the risks of side effects." MHRA advises that alternative vaccines should be offered to under 30s where available

8 Apr Australia, Belgium, France, and Italy announce restrictions on use of the vaccine

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