Battlefield Medicine

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Even though France is the country of Louis Pasteur, the French have long been reluctant to get themselves vaccinated. In the 1990s, the vaccine against hepatitis B was suspected of causing multiple sclerosis.[1] If the suspicion proved unfounded, the anxiety it provoked proved unyielding. It is no surprise that when it came to COVID-19, the French remained distrustful. In December 2020, some forty percent of the French public were prepared to accept vaccination; at the end of January 2021, sixty percent.[2] The roll-out of the Pfizer-BioNTech mRNA vaccine was, in any case, glacial in pace: 1.6 million doses were available in France on February 1, 2021. This was a full month *after* the start of the vaccination campaign, which began officially on December 27, 2020. Both general practitioners and pharmacists have traditionally been allowed to administer vaccines, but the mRNA vaccines—Pfizer and Moderna—require deep refrigeration, and neither the general practitioners nor the pharmacists were in a position to provide it.

A more practical vaccine was needed.

Enter AstraZeneca.

Viral vectored, solid, old-fashioned, and, it was hoped, reliable, the AstraZeneca vaccine does not require deep refrigeration. If stored at between two and eight degrees Celsius, it could keep for at least six months.[3] By comparison, the Pfizer vaccine can be kept for up to thirty days, but only if stored at between minus ninety and minus sixty degrees Celsius and replenished with dry ice every five days. Before use, it must be thawed, after which it can be kept for five days, but only if stored at between two and eight degrees Celsius. Each Pfizer vial holds enough for six doses, which must be used within six hours, compared to AstraZeneca's two doses for forty-eight hours.[4]

On January 29, 2021, the European Medicines Agency (EMA), an agency of the European Union that evaluates and supervises medicines, gave the all clear for the AstraZeneca vaccine.[5] On the same day it was approved, French president Emmanuel Macron questioned publicly whether the AstraZeneca vaccine should be restricted to those under sixty-five years of age, describing it as "quasi-ineffective" for anyone above this threshold.[6] "What I can tell you officially today," he remarked, "is that the early results we have are not encouraging for 60 to 65-year-old people concerning AstraZeneca."

Four days later, on February 2, 2021, the *Haute Autorité de santé* (*HAS*)—France's public health authority—recommended the AstraZeneca vaccine to "all citizens" and "all professionals in the health, medico-social and social sectors."[7] Yet that very same day, the *HAS* issued a press release in which AstraZeneca was recommended to the young and healthy, but not the elderly, noting that "the current data do *not* allow an assessment of the level of efficacy that this vaccine provides in people over 65 years of age."[8] The explanation given for these doubts was "the small number of participants aged 65 and over in the trials."

In the space of four days, two agencies—one European, one French—and the French president had offered differing assessments on the efficacy and potential limitations of the AstraZeneca vaccine. The inevitable result of this mixed messaging from the authorities was confusion among the public concerning the vaccine.

It was against this uncertain background that AstraZeneca vaccinations began. As it turned out, the French public did not have to wait long for further conflicting assessments to emerge. On February 11, 2021, the *ANSM* (*L'Agence nationale de sécurité du médicament et des produits de santé*) noted that for every 10,000 individuals injected, roughly 150 of them suffered a number of flu-like symptoms.[9] The ANSM report created tremendous anxiety, particularly among nurses: "AstraZeneca … is a fine vaccine for the general public," observed Thierry Amouroux, spokesperson for France's national nurse union, "but for a population as exposed as healthcare workers, it is among the three least effective of the authorized vaccines."[10]

A month later, the news was even worse. On March 16, 2021, the EMA issued a press release concerning a possible link between the AstraZeneca vaccine and episodes of thrombosis.[11] Flu-like symptoms are one thing; thrombosis, another. A blood clot wandering to the brain, the heart, or the lungs may well prove fatal. Nonetheless, the EMA was still persuaded that "the vaccine's proven efficacy in preventing hospitalisation and death from COVID-19 outweighs the extremely small likelihood of developing

[blood clots]." To put this into perspective, an article published by the *BMJ* on March 11 noted that just "30 cases of thromboembolic events had been reported among the five million people given the AstraZeneca vaccine in the European Economic Area."[12]

Given the initial advice from the EMA, France chose not to immediately suspend the AstraZeneca vaccination campaign. In Germany, AstraZeneca vaccinations had already been suspended on March 15 as a precautionary measure, on the advice of the Paul Ehrlich Institute, the country's vaccine authority.[13] The real shock came just two days later on March 17 when the *Élysée* backtracked on their decision to stand by the AstraZeneca jab—an about-face that did nothing to reassure the French public. Speaking off the record, a source in Macron's administration admitted that Berlin's earlier decision had a "psychological impact" on the French government.[14]

The EMA initially appeared confused as to just which principles its member states were appealing to in suspending the vaccine. On March 18, the EMA's executive director, Emer Cooke, fielded a question regarding the possibility of "harmonizing the application of the precautionary principle," which she diplomatically deflected, responding that, "There's a lot of things that we need to do to make sure that everybody has the same information about the benefits and risks."[15] The ambassador of the European Union (EU) to the United Kingdom, João Vale de Almeida, had other ideas. "When there are doubts, the principle of precaution prevails," he remarked on March 16.[16] And he was not alone. "Acting on the precautionary principle, and pending receipt of further information," Ireland's Deputy Chief Medical Officer, Dr. Ronan Glynn, announced that, "the NIAC [National Immunisation Advisory Committee] has recommended the temporary deferral of the COVID-19 Vaccine AstraZeneca vaccination program in Ireland."[17]

The precautionary principle was formally adopted in the Maastricht Treaty of 1992. In essence, this article allows the EU to take preventative action in the case of risk—specifically, "when a phenomenon, product or process may have a dangerous effect, identified by a scientific and objective evaluation."[18] Swedish philosopher Per Sandin defined the precautionary principle as "*if* [emphasis original] there is a threat, which is uncertain, then some kind of action is mandatory."[19] The article is sufficiently vague as to allow the EU to take action even when scientific evaluation "does not allow the risk to be determined with sufficient certainty," as the EU themselves have noted.[20] In their short book on the precautionary principle, Gary Marchant and Kenneth Mossman make the point that

> [t]he treaty itself does not define or otherwise articulate the requirements of the precautionary principle, nor was any official explanation or definition of the precautionary principle provided during the process of its enactment into the European Treaty. It has therefore been left to the community institutions to define and apply the precautionary principle.[21]

In 2000, the European Commission released a communiqué that sought to "establish a common understanding of the factors leading to recourse to the precautionary principle and its place in decision making, and to establish guidelines for its application based on reasoned and coherent principles."[22] The document included a series of general principles for the application of the precautionary principle. Among them was a cost-benefit analysis that entailed

> comparing the overall cost to the Community of action and lack of action, in both the short and long term. This is not simply an economic cost-benefit analysis: its scope is much broader, and includes non-economic considerations, such as the efficacy of possible options and their acceptability to the public. In the conduct of such an examination, account should be taken of the general principle and the case law of the Court that the protection of health takes precedence over economic considerations.[23]

This dictates that the pros and cons of any decision made on the basis of the precautionary principle must be carefully weighed before any action is taken. In the case of the AstraZeneca vaccine, intervention in France meant halting an already unpopular vaccination drive, and an extraordinary number of wasted vaccines, whereas inaction would have meant the continued rollout of a vaccine that had already proved effective in helping curb the UK's spiraling COVID cases.[24] The decision should not have been hard to make. Alas, were the EU forced into a decision, perhaps it would have been this easy. The scenario that unfolded, in which each European country opted to decide on its own, was unforeseeable and inevitably created widespread doubt among the bloc's populations. This was first the choice of Denmark, then Iceland, then Norway. The crisis has affected all of Europe in much the same way and each member of the EU has applied the precautionary principle in just the same way as well.

Even before the concerns about a possible connection to blood clots began to appear in mid-March 2021, the AstraZeneca vaccine had already been singled out for criticism in France. At the beginning of March, a nurse's union expressed doubt that AstraZeneca was best adapted to those at high risk of exposure to the virus.[25] At the time, the government declared no reason for doubt and urged that, their concerns notwithstanding, healthcare workers should promptly be vaccinated with the AstraZeneca vaccine.[26]

By March 29, only forty-two percent of nurses in France had received one dose of the vaccine, compared to eighty percent of general practitioners, and twelve percent of the

general population.[27] The figures were no less shocking in mid-June, when French daily, *Le Monde*, gained access to a document from the *Assistance Publique–Hôpitaux de Paris* (Public Hospitals of Paris) suggesting that while ninety-one percent of general practitioners had received one dose, nonmedical staff, including nurses and caregivers, were still well behind at fifty-four percent.[28] This figure was always unlikely to increase rapidly since the European bulk-order strategy led to a shortage of vaccines.[29] The decision to use age as a cutoff for nurses, as well as for the general public, has not helped matters. Using the risk of viral exposure would have made for a more logical strategy with respect to nurses. Anyone working in intensive care should have been first in line for vaccination regardless of age. During the first wave, contamination was directly linked to exposure. Beyond that, the problem is rooted in community transmission, with most hospital personnel becoming infected outside the hospital, at private gatherings.[30]

Accelerating the vaccination campaign means getting vaccinations done quickly in the hope that hospitalizations for COVID-19 decrease. Israel is a model. The symbolic threshold of 4,000 patients in ICU (intensive care units) was passed in France on March 15, exceeding the peak of the second wave. It was not until May 21 that this figure dropped below 4,000 patients once again.[31] The decision to suspend AstraZeneca means that hospitals have been forced to throw away doses of ready-to-use vaccines and to cancel appointments for vaccination.[32] To compensate, physicians have been told to extract a seventh dose of Pfizer from vials initially earmarked for five doses.[33]

As infection rates and ICU admissions remain high, it is clear that France and Europe must continue to accelerate the vaccination drive. The sooner we vaccinate, the sooner any vaccine hesitancy will be eased. To stop vaccinating for forty-eight to seventy-two hours in the name of the precautionary principle is to start work again on vaccine awareness from scratch. Any decision taken must take into account the risk-benefit balance that is largely in favor of *all* of the vaccines available to date. Their effectiveness, as research in both Europe and the US has shown, is, by definition, greater than fifty percent.[34] As a result, the AstraZeneca vaccine has been stigmatized and patients who know nothing of even the simplest risk-benefit calculation are now demanding the right to choose their vaccines.[35]

At the beginning of the pandemic, masks were initially declared to be of no use, and then made mandatory indoors—and then made mandatory outdoors, but only in the summer of 2020. As the first wave swept across Europe in early 2020, France carried out fewer COVID tests than most other countries in Europe,[36] finally screening everyone who wanted to be tested free of charge, including those who were asymptomatic and without a prescription, by September 2020.[37]

It is always easy to see things better backwards, but perhaps a Europe-wide decision should have been applied from the start. The precautionary principle might have suggested that given the real risk of disease and death, all of Europe should have been placed under strict quarantine. If this is well-known as a medieval strategy, it is no less effective for that. No matter the virus, either it dies with its host or its host outlives it; if it cannot spread, it cannot survive. If a complete and effective quarantine is economically unfeasible, the confusion created by the AstraZeneca debacle was unacceptable in a public health crisis—the French government both declaring that the AstraZeneca vaccine is safe in view of the benefit-risk balance of the vaccine, and then, 48 hours later, declaring that, since Germany has applied the precautionary principle, so we will also apply it. The AstraZeneca vaccine is now tainted, and will remain a second-rate vaccine in the eyes of the public, if only because the French, at least, remember that questions have been raised about its efficacy and potential undesirable effects.[38]

It is always safe enough in France to blame any muddle on a failure of communication. The possible effects of the vaccine may not have been sufficiently explained; and no one in government has clearly made the distinction between individual risk and collective welfare. The risk of thrombosis provoked by the AstraZeneca vaccine is *lower* than the risks of thrombosis observed in young smokers taking estrogen-progestogen birth control pills.[39] On the other hand, patients suffering COVID-19 infection run an absolutely clear and significantly increased risk of thromboembolic events.[40] The cost benefit assessment is entirely in favor of AstraZeneca vaccination. Recent data analysis from a team at Oxford shows a thirty-nine-in-one-million chance of developing thrombosis in the two weeks following a COVID-19 diagnosis.[41] In the fortnight following a Moderna or Pfizer jab, the same study has shown that this figure drops to four in a million, while the current EMA estimate holds the chances of thrombosis from the AstraZeneca jab at the slightly less favorable five in a million. The scales of profit-risk are leaning heavily to one side. The risk-benefit balance is overwhelmingly in favor of vaccination.

What is new and specific to this epidemic is the association of vaccine and laboratory names. More and more people are calling vaccination centers to ask for the name of their vaccine. The world's geography is now at issue, with vaccines appearing from America, England, Russia, and China. Cost plays a role in all this. It always does. Pfizer and Moderna vaccines are the most expensive at nineteen US dollars and fifty cents, and fifteen dollars per shot, respectively.[42] It is not in the interests of France, nor of Europe, to suspend AstraZeneca vaccinations. AstraZeneca is fourfold less expensive than the mRNA vaccines. Seven million doses of Johnson & Johnson's Janssen vaccine and thirty-five million Pfizer doses are scheduled to

arrive in France by the end of the summer. There is no time to wait for one vaccine to be replaced by another of equivalent quality, and that is a real concern. In the end, it is the opposite of what France experienced in 2009 with the H1N1 pandemic, when Roselyne Bachelot, the minister of health at the time, ordered double the amount of required vaccines after failing to follow the up-to-date advice that booster doses were not necessary.[43] Fortunately, the H1N1 pandemic did not hit Europe as expected, and this mistake did not influence public opinion.

What is to be done now, and in the future when the next pandemic comes along? We need something stronger than the current sanitary advertisements in which a grandmother kisses her markedly unenthusiastic grandchildren because she has been vaccinated. To break the chain of transmission, it is not enough to attend to the elderly. Israel began vaccinating sixteen- to-eighteen-year-olds in late January 2021,[44] and, in mid-May, began preparations to vaccinate twelve- to-fifteen-year-olds.[45] There must be, above all, a rediscovery of decision-making principles that have, at least, some clear content. Something like a collective sanitary benefit really exists. A good example of the individual benefits associated with vaccination is the vaccine passport that was implemented in Europe during July 2021. The adoption of the vaccine passport offers a route to return to normal life, free of restrictions. What is crucial in promoting a collective benefit is not exclusively the effectiveness of a vaccine in protecting symptomatic forms of a disease. It is a matter of eliminating the virus in the first place. This cannot be done on the basis of any kind of individual risk assessment.

A final note of caution is, perhaps, warranted. Humanity has been lucky with respect to COVID-19. Some diseases are far more lethal, but spread slowly. Although COVID-19 spreads rapidly, it is not terribly lethal.

The next pandemic may be both.

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