



Unveiling the interplay between evidence, values and cognitive biases. The case of the failure of the AstraZeneca COVID-19 vaccine

M. Cristina Amoretti PhD¹ | Elisabetta Lalumera PhD²

¹DAFIST, Philosophy Section, University of Genoa, Genoa, Italy

²Department for Life Quality Studies, University of Bologna, Rimini, Italy

Correspondence

M. Cristina Amoretti, PhD, DAFIST, Philosophy Section, University of Genoa, via Balbi 4, 16126 Genoa, Italy.
Email: cristina.amoretti@unige.it

Abstract

This paper depicts a Covid science case, that of the AstraZeneca Vaxzevria vaccine, with specific focus on what happened in Italy. Given that we believe acknowledging the role of non-evidential factors in medicine is an important insight into the recent philosophy of science, we illustrate how in the case of Vaxzevria, the interplay between facts, values (both epistemic and non-epistemic) and cognitive biases may have possibly led to different institutional decisions based on the same evidence. The structure of the paper is as follows. First, we provide a glossary of the relevant terms involved, that is to say, epistemic values, non-epistemic values and cognitive biases. Second, we sketch a timeline of Vaxzevria's approvals and suspensions by relevant institutional healthcare authorities with special focus on Italy and the Italian Medicines Agency. Then we show the interplay between the evidence base, epistemic as well as non-epistemic values and cognitive biases using a narrative review of political decisions along with newspaper and social media content pertaining to Vaxzevria. We briefly compare Italy with other European countries to show that different political decisions were made on the basis of the same evidence.

KEYWORDS

cognitive bias, communication, COVID-19, philosophy of medicine, vaccination, values in science

1 | INTRODUCTION

The AstraZeneca COVID-19 vaccine (AZD1222), also known as Vaxzevria, received conditional marketing authorisation from different agencies between December 2020 and February 2021 and was recommended for all age groups over 18. However, a series of events occurred in subsequent months—including reports of adverse effects, miscommunication and disputes between AstraZeneca and institutions—which resulted in suspensions, partial re-authorisations

with assorted types of restrictions and definitive bans on the vaccine in some countries. This variety and heterogeneity of institutional decisions based on the same evidence caused a loss of trust not only in Vaxzevria but all COVID-19 vaccines.¹ Given public trust has been identified as a key element in vaccination uptake, its disruption is to be considered harmful to the whole population² and its causes deserve to be further explored. As we believe that acknowledging the role of non-evidential factors in medicine is an important insight into the recent philosophy of science, we describe the example of

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2023 The Authors. *Journal of Evaluation in Clinical Practice* published by John Wiley & Sons Ltd.



Vaxzevria as a case where institutional decisions may be regarded not only as evidence-based, but also value-laden, and perhaps partly cognitively biased.

The structure of the paper is the following. First, we provide a glossary of the relevant terms involved, that is to say, epistemic values, non-epistemic values and cognitive biases. Second, we sketch a timeline of Vaxzevria's approvals and suspensions by institutional healthcare authorities, focusing on the Italian Medicines Agency (AIFA). Then we show the interplay between the evidence base, epistemic and non-epistemic values and cognitive biases, through a narrative review of political decisions as well as newspaper and social media content relating to Vaxzevria. Focusing on the case of Italy, we briefly compare it with other European countries to show that different political decisions have been made based on the same evidence. Our main aim is to expose how epistemic and non-epistemic values and cognitive biases may have been integrated with the evidence and possibly led to disagreement regarding guidelines and health policies. To conclude, we argue that to restore and promote public trust in Vaxzevria, vaccines, and more generally in medicine, such an interplay between evidence, values, and cognitive biases should be disclosed, made explicit, and publicly discussed.

2 | EPISTEMIC VALUES, NON-EPISTEMIC VALUES AND COGNITIVE BIASES

As a preliminary step, we provide a glossary of the relevant terms involved.

First, epistemic values can be conceived as properties of a hypothesis or theory that are indicative of its truth (or truth-likeness) and are then directly linked with the pursuit of knowledge: 'accuracy, consistency, scope, simplicity and fruitfulness' (ref. 3, 322), objectivity, error reduction, effectiveness, robustness, predictive power, novelty, applicability, ontological uniformity, unification, explanatory power and external coherence are some examples. Although not all philosophers endorse the same list of epistemic values nor the same ways of ranking and applying them, these values, being truth-conducive, are not considered problematic for the scientific enterprise.

Non-epistemic values, on the other hand, are linked to practical aims, and then seem to be disconnected from the pursuit of knowledge. They may include moral values (such as safety, beneficence, non-maleficence and autonomy), political and social values (such as sustainability, equality, inclusion and justice), economic values (such as feasibility and profit), personal values (such as individual pleasure) and so on. While traditional—that is, logical empiricist—philosophy of science held that science is and ought to be free of non-epistemic values, many contemporary philosophers have provided arguments to the effect that science neither is nor should be free of them.^{4,5} Historically, the debate about non-epistemic values started with the work of Rudner,⁶ who acknowledged that values are necessary to determine what is deemed to be sufficient evidence. Specifically, Rudner argued that because science is not a

deductive process and there is always an inductive gap between the evidence and the hypotheses formulated in a scientific field, scientists must decide whether the available evidence is strong enough, or the probability is high enough, to warrant the acceptance of a certain hypothesis weighting 'the importance, in the typically ethical sense, of making a mistake in accepting or rejecting the hypothesis' (ref. 6, 2). Thus, non-epistemic values can be used as reasons for accepting, or refuting, a certain hypothesis. This possibility, of course, opens up the question of how to distinguish 'good' reasons (i.e., reasons that are truth-conducive or influence decisions in a legitimate and rational way) from 'bad' reasons (i.e., reasons that deviate from truth or compromise decisions).⁷ Although it is not possible to dwell on this point, some very general possibilities are: (1) leave the discussion to experts within specific communities (doctors, philosophers, politicians and so on); (2) open the discussion to the public and relevant stakeholders.⁸

Finally, cognitive biases are typically defined as cognitive processes that systematically deviate from the recognised norms of logic and rationality and, in so doing, affect our judgement and decision-making. Typically, cognitive biases are described as predictable (they can be expected to appear under certain circumstances), universal (they affect all human beings), tenacious (they tend to affect even those who know them) and unconscious (they are cognitive processes of which the subject is unaware). In the medical field, more than a hundred cognitive biases have been detected, both in research and in the clinic.^{9–11} Some examples are the availability bias, that is, the tendency to judge things as being more likely, or frequently occurring, if they readily come to mind; the confirmation bias, that is, the tendency to look for confirming evidence to support a hypothesis rather than look for disconfirming evidence to refute it; the expectation bias, that is, the tendency to provide outcomes in accordance with what is expected and the ascertainment bias which occurs when prior expectations (e.g., stereotyping and gender bias) affect our judgement. Given that they are rooted in unconscious thought processing, cognitive biases cannot be regarded as reasons, either good or bad,¹² but it remains an open question whether or not they may have some epistemic benefits in specific circumstances, for example, when they work as heuristics.¹³ For instance, the representativeness bias, which dubs the tendency to make decisions based on a prototypical case (prototypical reasoning), may be epistemically beneficial in cases where prompt diagnosis is required despite limited access to knowledge, such as in emergency situations or in the emergency department.¹⁴ Cognitive processes based on prototypical reasoning are in fact typically fast, automatic and cognitively undemanding.

3 | VAXZEVRIA: A LONG STORY SHORT

Vaxzevria was developed by the Anglo-Swedish pharmaceutical company AstraZeneca for people 18 years of age and older for the purpose of preventing the development of COVID-19 in the event of infection with the SARS-CoV-2 coronavirus. The vaccine contains an

adenovirus specially modified to carry DNA molecules, which the human body is then able to use to temporarily produce the SARS-CoV-2 spike protein. Obviously, the spike protein does not cause COVID-19 and the adenovirus cannot reproduce or cause any viral disease. The first emergency supply authorisation for people over the age of 18 was granted in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA) on 30 December 2020.¹⁵ Following this, the EMA, the AIFA, the World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) and Canada's National Advisory Committee on Immunization (NACI) also granted conditional authorisation for people over 18 years of age—on 29 January, 30 January, 10 February and 26 February 2021, respectively.^{16–19}

Putting aside questions regarding the efficacy of Vaxzevria, whose use in countries such as Italy was initially restricted to people under the age of 55, two other important issues soon emerged in relation to the vaccine.

First, thanks to pharmacovigilance, around mid-March 2021, the first suspected cases of thrombosis were reported in Europe, mainly in women between the ages of 25 and 60. At that time, however, a causal connection between the vaccine and the blood clots had not yet been confirmed, and on 18 March, the EMA²⁰ reassured the European population that the benefits of the Vaxzevria vaccine continued to far outweigh the risk of side effects. After further analysis, on 7 April, another statement by the EMA²¹ confirmed that with respect to the use of Vaxzevria, the risk-benefit ratio remained positive overall, but also specified that blood clots associated with low platelet levels should be listed as a very rare side effect of the vaccine. That said, the authorisation regarding Vaxzevria remained unchanged for all people over 18 years of age.

Second, a quarrel between the EU and AstraZeneca began on 24 January 2021, with AstraZeneca announcing 'a bottleneck' in the delivery of its vaccine to EU states (but not the United Kingdom) so that only a third of the planned quantity of vaccine doses would be supplied. At the same time, AstraZeneca announced that they were reserving vaccine doses produced in the United Kingdom for the United Kingdom only, due to differences in the contracts that the United Kingdom and the EU had signed. More precisely, Pascal Soriot, AstraZeneca's CEO, declared that the agreement with the EU should be understood as the 'best effort' possible on the part of the Anglo-Swedish company and not as a 'contractual commitment' regarding a precise number of vaccine doses.²² As a result, on April 21, the EU officially started a legal dispute with AstraZeneca regarding the non-delivery of vaccine doses under the contract, while on 10 May, it announced that no new orders of Vaxzevria would be placed. The dispute between the EU and AstraZeneca lasted until 3 September, when the parties finally reached an agreement with respect to the vaccine doses to be delivered to EU member states.²³

With these considerations in mind, we will concentrate on the case of Italy, where between February and June 2021, health policies underwent rather significant changes. The minimum age for receiving Vaxzevria was originally set at 18 with an upper limit of 55

(30 January 2021), but the latter was then raised to 65 (22 February) and then eventually scrapped (8 March). The administration of Vaxzevria was suspended by the government on 16 March as a precaution after the first suspected cases of thrombosis. Nonetheless, just 2 days later on 18 March, after assurances from the EMA and the AIFA,²⁴ regular Vaxzevria administration resumed.²⁵ However, the emergence of more cases of thrombosis prompted the government to 'suggest' in a statement on 7 April that Vaxzevria be administered only to individuals over 60 and those who were scheduled to receive their second dose.²⁶ In spite of this, in May, a few regions chose to implement so-called 'open days' to allow people over the age of 18 to book vaccination using the AstraZeneca vaccine (or alternatively the Johnson & Johnson one) without having to wait until the opportunity to book a COVID-19 vaccine had also been offered to their age group. In Italy, aside from some 'at risk' categories, vaccination priority was established on the basis of age so that younger individuals would have been the last to receive the jabs if the open days had not been available. Following a number of deaths from thrombosis in subjects vaccinated with Vaxzevria, and in particular, the death of a young woman from Liguria, the government decided to suspend all regional open days on 14 June. They also mandated that nobody under the age of 60 be vaccinated with Vaxzevria, whether the first or second dose.²⁷ This measure effectively mandated heterologous vaccination for all those under the age of 60 who had received the first dose of Vaxzevria. This decision was altered a few days later when the option was left open for those who had received the first dose of Vaxzevria to choose between heterologous vaccination or not.²⁸ To sum up, vaccination with Vaxzevria was then reserved only for people over 60 years of age and, even though it was not recommended, for second doses.

Against the backdrop of the EMA's general guidelines, which warn about the possibility of blood clots but do not recommend any specific suspensions or restrictions on age and/or second doses, other European countries reacted differently over the same time period. Most of them suspended the vaccine in mid-March, only to resume it on 19 March, following the EMA's initial reassurance, and eventually decided to limit its use to people over 55 (e.g., Belgium) or 60 (most of the others). Some countries also recommended or imposed heterologous vaccination for younger people. Denmark, in addition to being the first European country to halt the administration of Vaxzevria (11 March), also chose to discontinue its use entirely (14 April) regardless of age, gender or use as a second dose.²⁹ The same decision was also made by Norway.

In the United Kingdom, during the period between March and April 2021, when most European countries suspended and then restricted the use of Vaxzevria, the vaccine was never withdrawn from circulation, nor was its use restricted to people over a certain age.³⁰ However, as the rare cases of cerebral venous thrombosis appeared to be more likely to occur in younger people, the MHRA decided in early April to offer adults under 30 an alternative to Vaxzevria, allowing them to choose which vaccine they would be vaccinated with.³¹ On 7 May, the offer of an alternative option became available also to adults under the age of 40.³²



What factors help to explain the sometimes contradictory decisions summarised above? To answer this question, we believe that it is not sufficient to consider only the evidence provided by medical research, since the intertwining of epistemic and non-epistemic values as well as cognitive biases, appears to be involved.

4 | EPISTEMIC FACTORS

The overall efficacy and safety of Vaxzevria are based on an analysis of aggregate data from four phase I/II, II/III and III clinical trials conducted in the United Kingdom, Brazil and South Africa,³³ as well as data from an additional phase III clinical trial conducted in the United States, Peru and Chile. When Vaxzevria was approved, 56,124 participants aged 18 and above had been randomised, with 33,869 receiving at least one dose of Vaxzevria and 31,217 receiving two doses.^{34,35} However, after commercialisation, some significant and extremely rare (<1/10,000) cases of thrombosis with thrombocytopenia syndrome were documented.³⁶ These included both venous thrombosis, such as cerebral venous sinus thrombosis and splanchnic vein thrombosis, as well as arterial thrombosis.

The evidence supporting Vaxzevria's efficacy and safety comes from randomised control trials (RCTs), the type of experimental studies that are traditionally placed just below the apex of the Evidence-Based Medicine evidence pyramid.³⁷ In contrast, the very rare cases of severe blood clots associated with thrombocytopenia reported following Vaxzevria use, particularly in women under the age of 55, were initially documented by case reports and case series, and were later supported by mechanistic evidence. For instance, molecular investigations, not randomised controlled trials, have highlighted a putative mechanism underlying 'vaccine-induced prothrombotic immune thrombocytopenia': an antigen or protein produced by the vaccine would activate platelets to initiate clotting, similar to what occurs in so-called 'heparin-induced thrombocytopenia'.³⁸

It follows, then, that different policies with respect to the use of Vaxzevria may have been partially influenced by different ways of assessing what counts as best or adequate evidence and establishing causal claims, that is, on epistemic values. If, for example, one maintains that more weight should always be assigned to evidence from RCTs, one must then conclude that, at the time of the first case reports, there was insufficient evidence to establish a causal connection between Vaxzevria and blood clots associated with thrombocytopenia. In this case, further restrictions on the use of Vaxzevria would not have been fully justified. If, on the other hand, anecdotal (case reports) and mechanistic evidence are considered on a par with RCTs, it can then be agreed that there was already sufficient evidence to suggest the presence of a causal mechanism linking Vaxzevria to blood clots. If this is the case, cautionary limitations on the use of Vaxzevria would have been partly justified.

The different ways of assessing the available evidence and establishing causal claims are currently debated within philosophy of medicine.^{39,40} Some claim that to prove a causal relationship, one must understand the mechanism causing an effect (or the

pathophysiological rationale). Contrarily, those who view causality as a correlation do not see the mechanism as necessary proof. In this view, a good RCT is always the best evidence for establishing causal claims. In our scenario, the distinction can be seen in whether or not the data from individual blood clot occurrences should count as evidence along with the RCT's findings, for establishing a causal link between the vaccine and the adverse event.

5 | NON-EPISTEMIC FACTORS

Compared to the situation in 2020–2021, we now possess more evidence. On the one hand, there are studies that show that the RCTs that led to the approval of vaccines, and of Vaxzevria in particular, did not sacrifice safety because of time or market pressure. Even though these trials were the fastest ever conducted and used a different methodological design than standard RCTs—they were so-called 'adaptive trials'—the most recent evaluations agree that they provide strong evidence, even suggesting that they could serve as a model for future trials.^{41–43} On the other, there is now additional evidence supporting a causal relationship between blood vaccinations and clot incidents. An analysis of 20 studies and 286 cases conducted recently concluded that 'Prompt recognition of COVID-19 vaccine as the causal agent of thromboembolism is warranted' (ref. 44, 7). The same authors state that it is also important to consider the fact that 'the reported rates of venous and arterial thromboembolism were 0.075 and 0.13 cases per 1 million persons vaccinated days, which was lower than the average thromboembolism risk in the general population' (ref. 44, 1). In other words, the evidence for determining that the vaccine is in fact the cause of thrombocytopenia in specific cases is different from the evidence for deciding whether the drug should be advocated for use in the general population to avoid COVID-19 infection, weighing the risk of either occurrence.

As the EMA stated in 2021, 'benefits outweigh the risks'.²¹ Such an assessment also involves non-epistemic values because the EMA and other authorities judged, and still hold, that preventing many people from contracting a very dangerous disease as COVID-19 is a more important goal (in non-epistemic terms) than protecting a small number of people from blood clots.

The presence of non-epistemic values to complete empirical evidence is a phenomenon that philosophers of science have examined extensively. As already mentioned, because we can only have a limited number of empirical controls (both in fact and in principle), there will always be some 'inductive risk' of making a mistake in accepting or rejecting a scientific hypothesis, that is to say of incurring a false positive if we accept a false hypothesis incorrectly, or a false negative if we reject a true hypothesis incorrectly. As a result, evaluating and accepting scientific hypotheses is a function not only of the empirical evidence available to us, but also of the importance—defined in ethical, political, social and economic terms—of accepting a false hypothesis or rejecting a true hypothesis.^{4,6} An example of inductive risk can be found in a text by Hill, one of the fathers of epidemiology. The case in point is an

observational study on the prevalence of a particular disease among workers in a nickel-processing factory. The hypothesis in question is that nickel exposure is associated with disease, and Hill argues that the consequences of a false positive (wrongly accepting it and requiring workers to stop exposing themselves to nickel) are less severe than those of a false negative (continuing to permit workers to expose themselves to nickel). In this case, a nonmaleficence principle is at work, that is, when in doubt, prioritise the option that will cause the least harm in terms of health.⁴⁵

Returning to our case, we said that the reasons why the vaccine was authorised despite evidence of a causal link with blood clots may have included an assessment of whether it is right, preferable and appropriate to protect many people with the Vaxzevria vaccination at the expense of failing to prevent some people, a very tiny percentage, developing blood clots. Of course, whether it is right, preferable, and appropriate to pursue the first aim over the second can be debated. The non-epistemic reasons can be evaluated inside the scientific community, but the debate can also be opened up to the general public. To our knowledge, the discussion over AstraZeneca's vaccine has never taken this form.

Another aspect to consider in connection with non-epistemic values is the external validity of drug trials. Trials are designed and conducted to maximise the generalisability of results, but—as highlighted above—this extrapolation can never be perfect. The eligibility criteria for participants are always narrow and, according to some critics, not inclusive—for example, pregnant women and elderly people are almost always excluded.^{46,47} This is tantamount to saying that adverse cases are ineliminable but also that efficacy may be more limited than claimed—which is why research takes time, and only reproducibility of studies guarantees better results. Thus, prioritising the speed of outcome, due to, for instance, the political urgency to provide solutions and market pressure, can be another way in which non-epistemic values kick in.

There are also other non-epistemic factors which may explain the different reactions to the same case reports of the adverse events of Vaxzevria in the United Kingdom, Italy and other EU countries. According to some scholars,^{1,48} adverse cases have been emphasised in some European countries—including Italy—partly because of AstraZeneca's economic disagreements with the governments of EU member states over promised supplies. This interpretation specifically emphasises the possible role of economic values such as profit.

Similarly, the low cost of Vaxzevria and its large, remaining unused stocks have been central economic factors that, combined with social values, such as younger people wishing to receive their vaccine jab earlier than it would normally have been scheduled to overcome travel restrictions and other social limitations, were instrumental in the decision made by some Italian regions to organise the 'open days' in the early May, despite the suggestion, made on 7 April, to reserve Vaxzevria for people over 60 and for second doses. All these factors, again, are clearly non-epistemic.

To sum up, non-epistemic considerations of an ethical, political, social and economic nature came into play in determining how much

empirical evidence was deemed sufficient to evaluate the efficacy and safety of Vaxzevria, and thus to decide to put it in the market. Similar considerations may have acted in balancing effectiveness and the need for quick approval by national medicine agencies. Of course, this does not mean that the evidence base was not adequate, good or sound enough, but rather that it was supplemented by non-epistemic values, which initially went unnoticed by the public. Although non-epistemic factors were in play, the discussion over Vaxzevria has never explicitly referred to them.

6 | COGNITIVE BIASES

To explain what happened in Italy in early June 2021, however, epistemic and non-epistemic values may not be sufficient. At that time, the available evidence indicated that the serious cases of thrombosis observed after the second dose of Vaxzevria were even rarer⁴⁹ and no RCTs were available on the efficacy and safety of heterologous vaccination—the first preliminary results were published at the end of the month.⁵⁰ Still, the Italian government on 14 June imposed heterologous vaccination for people under 60 years of age who had already received the first dose of Vaxzevria and then, just 4 days later, on 18 June, allowed the same group of people to choose between heterologous vaccination and Vaxzevria. How so?

In what follows, we illustrate five cognitive biases that may have played a role in the decision-making processes regarding Vaxzevria health policies. It is important to stress that these examples are merely meant to be inferences to the best explanation for certain observable behaviours rather than empirical claims detailing the real cognitive processes of specific real-world decision-makers.

First, let's consider the availability bias, that is, the tendency to overestimate the likelihood of those events that readily come to mind, are more recent, or have an unusual emotional charge. In this regard, it is important to mention that in Liguria in early June 2021, in a very short space of time, two young and healthy women died shortly after receiving a Vaxzevria jab. These events may have triggered the availability bias, which in turn may have contributed to overestimating the likelihood of the adverse effect. Thus, this bias may partially explain the decision to impose heterologous vaccination even though, at that time, the evidence for its efficacy and safety was still incomplete.

Second, confirmation bias describes the tendency to focus on information that confirms one's hypothesis or preconception rather than on information that disconfirms it. The triggering of this bias may have contributed to fallaciously considering the deaths of the two young and healthy Ligurian women as confirmations of the hypothesis of a causal link between Vaxzevria and blood clots, which in turn may partially explain further restrictions on the vaccine.

Third, the illusion of causality bias is the tendency to infer a causal link between a known event and another known subsequent event. For example, a teacher from Biella, in the Piedmont region, died on 14 March 2021, 1 day after receiving an AstraZeneca jab. The short time span between these two events (and other similar



ones) may have triggered the illusion of causality bias, which in turn may have contributed to reinforce the hypothesis of a causal link between Vaxzevria and death, and overestimate the likelihood of the adverse effect. This, again, may partially explain the imposition of heterologous vaccination.

Fourth, the framing effect describes the tendency of drawing conclusions from some information depending on how the information is actually presented. A quantitative study using language processing and network analysis shows that from March 2021, mainstream and social media content about Vaxzevria increasingly included words like 'thrombosis', 'threat', 'death' and 'dangerous'.⁵¹ The death of the teacher in March was reported by *Il Messaggero*, one of Italy's most widely read newspapers, with a brief headline implying a direct link between the two events: 'Teacher dies in Biella after vaccine jab. Lot ABV5811 suspended by Piedmont'. In early June 2021, all Italian newspapers and media framed the deaths of the two young women from Liguria in a similar way. Again, the triggering of this bias may have been partially responsible for reinforcing the idea of a causal link between Vaxzevria and death, and thus for imposing heterologous vaccination.⁵²

Fifth, the social conformity bias describes the tendency for people to change their behaviour, beliefs or decisions to match those of others in a larger group. As evidence did not change in a 4-day span, this bias may partly help to explain the June 18 backtrack, when the possibility of receiving a second dose of Vaxzevria was reinstated following the refusal by many people to accept heterologous vaccination.

These are but a few cognitive biases that may have contributed to the swift change in Vaxzevria-related health policies, but we deem them to be sufficient to show our point. Again, we are not claiming that cognitive biases are the only or even the main factors that need to be considered to account for the Italian government's health policies. Rather, we believe that these biases, along with epistemic and non-epistemic values, may have served to complete the available evidence. To put it differently, the empirical evidence may not be sufficient on its own to explain the different, and at times contradictory health policies that were put into place in a relatively brief period.

7 | CONCLUSIONS

If it is true that the variety of institutional decisions in the face of the same evidence caused a loss of trust in Vaxzevria and in all COVID-19 vaccines, then the source of these divergences deserves to be further investigated. The main aim of this paper was to show that these divergences may be explained by the fact that medical practices and health-related decisions are inevitably steeped in values and possibly influenced by cognitive biases. This, however, does not in any way mean that these practices and decisions are unreliable, corrupt or defective, nor that their rationality and objectivity should be denied, as many philosophers of science now convincingly argue. Still, we believe that unveiling, explaining and publicly discussing how specific

values and cognitive biases may contribute to the completion of the evidence base, is an important step towards a better understanding of why different political decisions and health policies can be advanced on the basis of the same evidence. Such an understanding, in turn, may be useful to restore and promote public trust not only in vaccination campaigns, but also in medicine and science more generally. On the other hand, ignoring the interrelationship between evidence, values and cognitive biases may lead to what has been dubbed 'a pandemic of nonsense'.⁵³ To conclude, our general aim was to use the case study of Vaxzevria to show how philosophical analysis can help to clarify the reasons for possible controversies arising over health policies, not only in the case of vaccination but also more broadly.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

ORCID

M. Cristina Amoretti  <http://orcid.org/0000-0003-2892-577X>

Elisabetta Lalumera  <http://orcid.org/0000-0002-0345-0838>

REFERENCES

1. Wise J. Covid-19: how AstraZeneca lost the vaccine PR war. *BMJ*. 2021;373:n921.
2. Larson HJ, Broniatowski DA. Volatility of vaccine confidence. *Science*. 2021;371(6536):1289.
3. Kuhn T. *The Essential Tension*. The University of Chicago Press; 1977.
4. Douglas HE. *Science, Policy, and the Value-Free Ideal*. University of Pittsburgh Press; 2009.
5. Longino HE. *Science as Social Knowledge*. Princeton University Press; 1990.
6. Rudner R. The scientist qua scientist makes value judgments. *Philos Sci*. 1953;20(1):1-6.
7. Holman B, Wilholt T. The new demarcation problem. *Stud Hist Philos Sci*. 2022;91:211-220.
8. Alexandrova A, Fabian M. Democratising measurement: or why thick concepts call for coproduction. *Eur J Philos Sci*. 2021;12(1):1-23.
9. Blumenthal-Barby JS, Krieger H. Cognitive biases and heuristics in medical decision making: a critical review using a systematic search strategy. *Med Decis Making*. 2015;35(4):539-557.
10. Hofmann B. Biases in bioethics: a narrative review. *BMC Med Ethics*. 2023;24(1):17.
11. Saposnik G, Redelmeier D, Ruff CC, Tobler PN. Cognitive biases associated with medical decisions: a systematic review. *BMC Med Inform Decis Mak*. 2016;16(1):138.
12. Amoretti MC, Lalumera E. Cognitive Biases in Medicine and the New Demarcation Problem.
13. Marewski JN, Gigerenzer G. Heuristic decision making in medicine. *Dialogues Clin Neurosci*. 2012;14(1):77-89.
14. Amoretti MC, Frixione M, Lieto A. The benefits of prototypes: the case of medical concepts. *Reti Saperi e Linguaggi Italian J Cognitive Sci*. 2017;4(1):97-114.
15. Medicines and Healthcare products Regulatory Agency (MHRA). Regulatory Approval of COVID-19 Vaccines AZ. REG 174

- Information for UK Healthcare Professionals. 30 December 2020. Updated 22 February 2021 and 15 April 2021. Accessed May 5, 2023. <https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca>
16. Agenzia Italiana del Farmaco (AIFA). Vaxzevria (ex COVID-19 Vaccine AstraZeneca). 2021. Accessed May 5, 2023. <https://www.aifa.gov.it/astrazeneca>
 17. European Medicines Agency (EMA). COVID-19 Vaccine AstraZeneca. 2021. Accessed May 5, 2023. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-covid-19-vaccine-astrazeneca_en.pdf
 18. Health Canada. Health Canada Authorizes AstraZeneca and Verity Pharmaceuticals Inc. Serum Institute of India COVID-19 Vaccines. 2021. Accessed May 5, 2023. <https://www.canada.ca/en/health-canada/news/2021/02/health-canada-authorizes-astrazeneca-and-verity-pharmaceuticals-inc-serum-institute-of-india-covid-19-vaccines.html>
 19. World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE). Interim Recommendations For Use of the ChAdOx1-S [recombinant] Vaccine Against COVID-19 (AstraZeneca COVID-19 Vaccine AZD1222 Vaxzevria™, SII COVISHIELD™). 2021. Accessed May 5, 2023. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1
 20. European Medicines Agency (EMA). Press Briefing on the Conclusion of the Investigation of COVID-19 Vaccine AstraZeneca and Thromboembolic Events by the Pharmacovigilance Risk Assessment Committee (PRAC). 2021. Accessed May 5, 2023. <https://www.ema.europa.eu/en/events/press-briefing-conclusion-investigation-covid-19-vaccine-astrazeneca-thromboembolic-events>
 21. European Medicines Agency (EMA). Press Briefing on the Conclusion of the Assessment of the Pharmacovigilance Risk Assessment Committee (PRAC) of Vaxzevria (Previously COVID-19 Vaccine AstraZeneca) and Thromboembolic Events. 2021. Accessed May 5, 2023. <https://www.ema.europa.eu/en/events/press-briefing-conclusion-assessment-pharmacovigilance-risk-assessment-committee-prac-vaxzevria>
 22. Guerrera A, Bolzen S, de Miguel R, Pascal Soriot. "There are a lot of emotions on vaccines in EU. But it's complicated" *la Repubblica*. 2021.
 23. AstraZeneca PLC. AstraZeneca and European Commission Reach Settlement Agreement over Vaccine Supply, Ending Litigation. 2021. Accessed May 5, 2023. <https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-and-european-commission-reach-settlement-agreement-over-vaccine-supply-ending-litigation.html>
 24. Agenzia Italiana del Farmaco (AIFA). After EMA's Opinion, Vaccinations with AstraZeneca to Resume Tomorrow. 2021. Accessed May 5, 2023. <https://www.aifa.gov.it/en/-/dopo-parere-ema-domani-riprendono-vaccinazioni-con-astrazeneca>
 25. Ministero della Salute. Circolare 19 marzo 2021—Vaccino Vaxzevria (precedentemente denominato COVID-19 Vaccine AstraZeneca). Aggiornamento raccomandazioni. 2021. Accessed May 5, 2023. https://www.aifa.gov.it/documents/20142/0/79231_1.pdf
 26. Ministero della Salute. Circolare 7 aprile 2021—Trasmissione nota AIFA sul parere di sospensione e revoca del divieto d'uso del vaccino Covid-19 AstraZeneca. 2021. Accessed May 5, 2023. https://www.aifa.gov.it/documents/20142/0/79629_1.pdf
 27. Ministero della Salute. Circolare 14 giugno 2021—Vaccinazione anti-SARS-CoV2/COVID-19. Trasmissione determina e parere AIFA sull'uso dei vaccini a mRNA per schedula vaccinale mista. 2021. Accessed May 5, 2023. <https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=81116&parte=1%20&serie=null>
 28. Ministero della Salute. Circolare 18 giugno 2021—Completamento del ciclo vaccinale nei soggetti sotto i 60 anni che hanno ricevuto una prima dose di vaccino Vaxzevria e chiarimenti sulle modalità d'uso del vaccino Janssen. Aggiornamento note informative e specifico consenso informato. 2021. Accessed May 5, 2023. <https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=81190&parte=1%20&serie=null>
 29. Danish Health Authority (DHA). Denmark Continues its Vaccine Rollout Without the COVID-19 Vaccine from AstraZeneca. 2021. Accessed May 5, 2023. <https://www.sst.dk/en/english/news/2021/denmark-continues-its-vaccine-rollout-without-the-covid-19-vaccine-from-astrazeneca>
 30. Medicines and Healthcare products Regulatory Agency (MHRA). UK Regulator Confirms that People Should Continue to Receive the COVID-19 Vaccine AstraZeneca. 2021. <https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca>
 31. Medicines and Healthcare products Regulatory Agency (MHRA). MHRA Issues New Advice, Concluding a Possible Link Between COVID-19 Vaccine AstraZeneca and Extremely Rare, Unlikely to Occur Blood Clots. 2021. Accessed May 5, 2023. <https://www.gov.uk/government/news/mhra-issues-new-advice-concluding-a-possible-link-between-covid-19-vaccine-astrazeneca-and-extremely-rare-unlikely-to-occur-blood-clots>
 32. Medicines and Healthcare products Regulatory Agency (MHRA). JCVI Advises on COVID-19 Vaccine for People Aged Under 40. 2021. Accessed May 5, 2023. <https://www.gov.uk/government/news/jcvi-advises-on-covid-19-vaccine-for-people-aged-under-40>
 33. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.
 34. World Health Organization (WHO). Background Document on the AZD1222 Vaccine Against COVID-19 Developed by Oxford University and AstraZeneca: Background Document to the WHO Interim Recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) Vaccine Against COVID-19 Developed by Oxford University and AstraZeneca. 2021. CC BY-NC-SA 3.0 IGO. Accessed May 5, 2023. <https://apps.who.int/iris/handle/10665/339882>
 35. World Health Organization (WHO). The Oxford/AstraZeneca COVID-19 Vaccine: What You Need to Know. 2021. Accessed May 5, 2023. https://www.who.int/news-room/feature-stories/detail/the-oxford-astrazeneca-covid-19-vaccine-what-you-need-to-know?gclid=Cj0KCQjwkbukBhDRARIsAALysV5mbpOQXDyUmvJkGmyFnGLOZv-Je3CVq6pQsHDwCUK-Glmc9R15LZW4aAkCcEALw_wcB
 36. European Medicines Agency (EMA). Signal Assessment Report on Embolic and Thrombotic Events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AstraZeneca (Other Viral Vaccines). 2021. Accessed May 5, 2023. https://www.ema.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid_en.pdf
 37. GRADE Working Group. Rating quality of evidence and strength of recommendations. *Br Med J*. 2004;328:1-8.
 38. de Gregorio C, Colarusso L, Calcaterra G, et al. Cerebral venous sinus thrombosis following COVID-19 vaccination: analysis of 552 worldwide cases. *Vaccines*. 2022;10(2):232.
 39. Howick J. *The Philosophy of Evidence-based Medicine*. Wiley-Blackwell; 2011.
 40. Parkkinen V-P, Wallmann C, Wilde M, et al. *Evaluating Evidence of Mechanisms in Medicine*. Springer; 2018.
 41. Kalinke U, Barouch DH, Rizzi R, et al. Clinical development and approval of COVID-19 vaccines. *Expert Rev Vaccines*. 2022;21(5):609-619.
 42. Ostropolets A, Hripcsak G. COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study. *BMJ Open*. 2022;12(8):e061126.



43. Wagner R, Hildt E, Grabski E, et al. Accelerated development of COVID-19 vaccines: technology platforms, benefits, and associated risks. *Vaccines*. 2021;9(7):747.
44. Mani A, Ojha V. Thromboembolism after Covid-19 vaccination: a systematic review of such events in 286 patients. *Ann Vasc Surg*. 2022;84:12-20.e1.
45. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58(5):295-300.
46. Amoretti MC, Vassallo N. Is there any problem with gender-specific medicine? *Verifiche*. 2013;42(1-3):139-156.
47. Rogers WA. Evidence based medicine and justice: a framework for looking at the impact of EBM upon vulnerable or disadvantaged groups. *J Med Ethics*. 2004;30:141-145.
48. Paglieri F. Mentire dicendo la verità: Trasparenza e cattiva comunicazione sui vaccini. il Mulino. 2021. Accessed May 5, 2023. <https://www.rivistailmulino.it/a/mentire-dicendo-la-verit-trasparenza-e-cattiva-comunicazione-sui-vaccini>
49. Bhuyan P, Medin J, da Silva HG, et al. Very rare thrombosis with thrombocytopenia after second AZD1222 dose: a global safety database analysis. *Lancet*. 2021;398(10300):577-578.
50. European Centre for Disease Prevention and Control. Partial COVID-19 Vaccination, Vaccination Following SARS-CoV-2 Infection and Heterologous Vaccination Schedule: Summary of Evidence. 2021. Accessed May 5, 2023. <https://www.ecdc.europa.eu/sites/default/files/documents/Partial%20COVID%20vaccination%20and%20heterologous%20vacc%20schedule%20-%202022%20July%202021.pdf>
51. Semeraro A, Vilella S, Ruffo G, Stella M. Emotional profiling and cognitive networks unravel how mainstream and alternative press framed AstraZeneca, Pfizer and COVID-19 vaccination campaigns. *Sci Rep*. 2022;12(1):14445.
52. Serafini L. The Covid-19 news narrative: The case of Italian Media. Proceedings of the 4th International Conference on Modern Approach in Humanities and Social Sciences. 2021. Accessed May 5, 2023. <https://www.dpublication.com/wp-content/uploads/2021/08/16-9926.pdf>
53. Mercuri M. A pandemic of nonsense. *J Eval Clin Pract*. 2022;28(6):927-931.

How to cite this article: Amoretti MC, Lalumera E. Unveiling the interplay between evidence, values and cognitive biases. The case of the failure of the AstraZeneca COVID-19 vaccine. *J Eval Clin Pract*. 2023;29:1294-1301. doi:10.1111/jep.13903