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Fast-tracking development and regulatory approval of COVID-19 vaccines in the EU: A review of ethical implications

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Abstract

The rapid spread of SARS-CoV-2 worldwide has triggered intense activity in the field of biotechnology, leading to the development and regulatory approval of multiple COVID-19 vaccines in less than 1 year while raising sustained scrutiny as to the ethical issues associated with this process. This article pursues a twofold objective. First, it reconstructs and provides a thorough overview of the different steps, from clinical trial design to regulatory procedures, underpinning the "fast-tracking" of COVID-19 vaccine R&D and approval. Second, drawing on a review of published literature, the article identifies, outlines, and analyzes the most ethically challenging aspects related to such process, including concerns around vaccine safety, issues in study design, the enrollment of study participants, and the challenges in obtaining valid informed consent. By scrutinizing relevant aspects of COVID-19 vaccine development and regulatory processes leading to market authorization, this article ultimately aims to provide a comprehensive overview of the regulatory and ethical issues underpinning the roll-out of this key pandemic-containment technology worldwide.

KEYWORDS

COVID-19 vaccines, R&D; ethical issues; fast-tracking; marketing authorization; regulatory process

1 | INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) was alerted of a cluster of cases of pneumonia of unknown cause in the city of Wuhan, People's Republic of China. Within a week, scientists identified the causative agent of the disease as a new type of coronavirus, later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The spread of SARS-CoV-2 rapidly became a Public Health Emergency of International Concern[1] and then a pandemic.[2] On January 11, 2020, the first draft genome was made publicly available, triggering intense global

[1]WHO. (2020, January 30). *Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)*. Retrieved April 12, 2022, from https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

[2]WHO. (2020, March 11). *WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020*. Retrieved April 12, 2022, from https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-COVID-19—11-march-2020

research and development (R&D) activity. Many laboratories and companies involved in such activity directed their efforts toward the development of a vaccine against Coronavirus disease 2019 (COVID-19). Two months later, in March 2020, the first phase 1 clinical trial of a vaccine was launched.[3] The remarkable pace of this scientific effort, which was made possible by substantial public funding, led to an achievement without precedent in the history of vaccines: the development, approval, and manufacturing of multiple vaccines in less than 1 year.

In Europe, the context on which this work focuses, the first vaccines to be authorized by the European Medicines Agency (EMA) were Pfizer-BioNTech's candidate vaccine (authorized on December 21, 2020), followed by Moderna's (January 6, 2021), AstraZeneca's (January 29, 2021), and Johnson & Johnson's (March 3, 2021). Underpinned by promissory expectations, COVID-19 vaccines came to epitomize the widespread recourse to 'techno-solutionist' modes of intervention to curb the spread of SARS-CoV-2[4] and became a cornerstone of pandemic containment strategies around the world.

Yet, aside from few emerging cases of patent malpractice,[5] the vaccines' fast-tracked R&D and approval process was itself fraught with concerns around the ethical and regulatory shortcuts that research conducted under stringent time pressure may entail.[6] Moreover, in spite of the breadth and reach of policy efforts, hesitancy toward COVID-19 vaccines has been persistent over the course of the pandemic,[7] not seldomly related to concerns around the unprecedented acceleration in vaccines' development and market authorization.[8]

Taking a cue from the expert debate unfolding in bioethics, research ethics, and cognate disciplines, this article sets out to (i) provide a detailed overview of the R&D and regulatory process underpinning the approval of the first four COVID-19 vaccines authorized in Europe and (ii) discuss the ethical implications underpinning such process.

The article is structured as follows: first, we provide some scientific background about the technology platforms used to develop the four vaccines under discussion; next, we analyze the factors that had the most influence in the acceleration of both the R&D and the regulatory approval process of the first four vaccines receiving marketing authorization by the EMA. Then, we conduct a review of published literature to identify, outline, and discuss the most ethically challenging aspects related to the vaccines' development and approval process, eventually leading to EMA's marketing authorization, including their possible ethical justifications. Supporting Information: Appendix 1 provides additional information about the clinical trials conducted for each vaccine under consideration and the resulting efficacy and safety data. Supporting Information: Appendix 2 lists the search strings. Supporting Information: Appendix 3 lists all the records that were included in the review of ethical issues.

By scrutinizing relevant aspects of COVID-19 vaccine R&D and approval, this article provides a comprehensive overview of the regulatory and ethical issues underpinning the roll-out of this key pandemic-containment technology worldwide, with a particular focus on the European situation and perspective. The ultimate aim is to provide an informed and nuanced understanding of a salient issue that has led to highly charged debates around vaccine policy.

2 | SCIENTIFIC BACKGROUND

The first four vaccines authorized for use by EMA relied on mRNA and viral vector technologies that have seldom or never been used to produce licensed vaccines. Unlike conventional vaccine platforms, these technologies do not contain the target virus or viral particles.[9] Rather, they both depend on nucleic acids (RNA or DNA) encoding the target antigen (the viral Spike (S) protein) used by the virus to enter host cells. These vaccines aim to induce neutralizing antibodies against the S protein, in order to prevent the interaction between the virus and the host cells.[10]

The therapeutic potential of viral vectors in the field of vaccines and gene therapy first started to be investigated in the 1970s. After showing promising results in preclinical and clinical studies, viral vectors have been used in the development of vaccines for epidemics, such as MERS, Influenza, Zika, and Ebola (in 2019, Ervebo was licensed in the EU to combat ebolavirus). Conversely, the use of mRNA as a therapeutic tool emerged in the early 1990s, but mRNA vaccines were not initially pursued, due to technological hindrances.[11] In the last decade, however, advances such as the introduction of next-generation sequencing (NGS), the increased capacity of nucleic acid synthesizers, the optimization of mRNA translation, stability, and delivery, together with substantial investments, allowed the mRNA vaccine field to make significant progress and place itself at the forefront of the response to the COVID- 19 pandemic.[12]

[3]Carvalho, T., Krammer, F., & Iwasaki, A. (2021). The first 12 months of COVID-19: A timeline of immunological insights. *Nature Reviews Immunology*, *21*(4), 245–256.
[4]Marelli, L., Kieslich, K., & Geiger, S. (2022). COVID-19 and techno-solutionism: Responsibilization without contextualization? *Critical Public Health*, *32*(1), 1–4.
[5]Thacker, P. D. (2021). COVID-19: Researcher blows the whistle on data integrity issues in Pfizer's vaccine trial. *BMJ (Clinical Research Ed.)*, *375*, n2635.
[6]London, A. J., & Kimmelman, J. (2020). Against pandemic research exceptionalism. *Science*, *368*(6490), 476–477.
[7]Lazarus, J. V., Ratzan, S. C., Palayew, A., Gostin, L. O., Larson, H. J., Rabin, K., Kimball, S., & El-Mohandes, A. (2021). A global survey of potential acceptance of a COVID-19 vaccine. *Nature Medicine*, *27*(2), 225–228; Neumann-Boehme, S., Varghese, N. E., Sabat, I., Barros, P. P., Brouwer, W., van Exel, J., Schreyögg, J., & Stargardt, T. (2020). Once we have it, will we use it? A European survey on willingness to be vaccinated against COVID-19. *The European Journal of Health Economics*, *21*(7), 977–982.
[8]Paul, K., Zimmermann, B. M., Corsico, P., Fiske, A., Geiger, S., Johnson, S., Kuiper, J. M. L., Lievevrouw, E., Marelli, L., Prainsack, B., Spahl, W., & Van Hoyweghen, I. (2022). Anticipating hopes, fears and expectations towards COVID-19 vaccines: A qualitative interview study in seven European countries. *SSM-Qualitative Research in Health*, *2*, 100035; Marelli, L. et al. (2021, March 26). Il vaccino anti-Covid e gli italiani. *Corriere Innovazione*, p. 26.
[9]Karpiński, T. M., Ożarowski, M., Seremak-Mrozikiewicz, A., Wolski, H., & Wlodkowic, D. (2021). The 2020 race towards SARS-CoV-2 specific vaccines. *Theranostics*, *11*(4), 1690–1702.
[10]Chung, Y. H., Beiss, V., Fiering, S. N., & Steinmetz, N. F. (2020). COVID-19 vaccine frontrunners and their nanotechnology design. *ACS Nano*, *14*(10), 12522–12537.
[11]Pardi, N., Hogan, M. J., Porter, F. W., & Weissman, D. (2018). mRNA vaccines-a new era in vaccinology. *Nature Reviews Drug Discovery*, *17*(4), 261–279.
[12]Defendi, H. G. T., da Silva Madeira, L., & Borschiver, S. (2022). Analysis of the COVID-19 Vaccine development process: An exploratory study of accelerating factors and innovative environments. *Journal of Pharmaceutical Innovation*, *17*, 555–571; Dolgin, B. E. (2021). The tangled history of mRNA vaccines. *Nature*, *597*(Sep), 318–324; Erasmus, J. H., & Fuller, D. H. (2020). Preparing for Pandemics: RNA Vaccines at the Forefront. *Molecular Therapy*, *28*(7), 1559–1560; Pardi, N., et al., op. cit. note 11.

3 | FAST-TRACKING THE R&D AND REGULATORY APPROVAL PROCESS

The extremely fast development of COVID-19 vaccines stemmed from the combination of several factors and innovations, both at the R&D and approval stages.[13] In what follows, we chart key factors related to the R&D process (Section 3.1) and the regulatory process leading to marketing authorization (Section 3.2).

3.1 | R&D process

3.1.1 | Clinical trial design

Trials were launched exceptionally early, just a few days after the WHO had declared COVID-19 a pandemic (March 11, 2020), as scientists could leverage knowledge (e.g., on the immunogenic potential of Spike proteins[14]) from years of previous research on similar coronaviruses, such as SARS-CoV-1 and MERS-CoV (Middle East Respiratory Syndrome Coronavirus).[15]

Clinical trials were also designed in a more flexible way, compared to the traditional sequential protocols. Under normal circumstances, vaccine trials take at least 6 years to be completed.[16] In a situation of a global health emergency, time compression was achieved by overlapping trial phases, running them in parallel (often in different parts of the world), or even combining them (Phase 1/2 trials to directly test safety on larger groups or Phase 2/3 trials to simultaneously test safety and efficacy).[17] A more detailed overview of the clinical trials conducted for each vaccine can be found in Supporting Information: Appendix 1.

3.1.2 | Availability of suitable technological platforms

In addition, when the pandemic struck, the vaccine research field was already preparing to face a potential threat from an unknown pathogen, also referred to as "Disease X." In 2018, the WHO first included Disease X in its list of priority pathogens, defining it as "the knowledge that a serious international epidemic could be caused by a pathogen currently unknown to cause human disease," and stressed the need for novel development and manufacturing platforms that could be readily adapted to new pathogens. Many biotech companies, therefore, were already investigating new vaccine approaches and had identified DNA- and RNA-based platforms as the ones that demonstrated the greatest potential for speed and a huge flexibility in terms of antigen manipulation.[18] DNA and RNA can be rapidly synthesized in vitro, all enzymes and reaction components can be easily obtained from commercial suppliers, and the manufacturing process is sequence-independent, so it can be standardized to produce nearly any encoded protein immunogen.[19]

A great contribution to vaccine development came also from cancer research, immunology, and gene therapy, as technologies such as mRNA were starting to prove their potential in these fields well in advance of the pandemic outbreak.[20]

3.1.3 | Ethics review and global cooperation

Research Ethics Committees (RECs) were also involved in significantly fast-tracking their reviewing process. In May 2020, the WHO published a series of guidelines, urging all RECs to prepare for the review of multiple projects in a very short time by, for example, contacting experts in advance and setting up systems for remote discussions. The guidelines also provided specific indications about the deadlines to respect in the reviewing process, compressing it to a few days.[21]

Global cooperation, within and between the scientific community, governments, and international organizations, was also paramount to fast-track vaccine R&D. The genomic sequence of SARS-CoV-2 was deposited in the NIH-operated GenBank database under an open-access license.[22] International partnerships were formed, including ACT (Access to COVID-19 Tools) Accelerator, launched by the WHO, and ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines), coordinated by the NIH.

3.1.4 | Public funding

Developing a new vaccine entails considerable financial risks. When it comes to risk-taking in innovation, early-stage public investments

[13]Bloom, D. E., Cadarette, D., Ferranna, M., Hyer, R. N., & Tortorice, D. L. (2021). How new models of vaccine development for COVID-19 have helped address an epic public health crisis. *Health Affairs*, *40*(3), 410–418; Kamble, P. H., & Dubhashi, S. P. (2020). Expedited COVID-19 vaccine trials: A rat-race with challenges and ethical issues. *Pan African Medical Journal*, *36*, 1–6.

[14]Sharma, O., Sultan, A. A., Ding, H., & Triggle, C. R. (2021). A review of the progress and challenges of developing a vaccine for COVID-19. *Frontiers in Immunology*, *11*(Oct), 1–17.

[15]Defendi, et al., op. cit. note 12; Doulberis, M., Papaefthymiou, A., Kotronis, G., Gialamprinou, D., Soteriades, E. S., Kyriakopoulos, A., Chatzimichael, E., Kafafyllidou, K., Liatsos, C., Chatzistefanou, I., Anagnostis, P., Semenin, V., Ntona, S., Gkolia, I., Papazoglou, D. D., Tsinonis, N., Papamichos, S., Kirbas, H., Zikos, P., … Kountouras, J. (2021). Does COVID-19 vaccination warrant the classical principle "ofelein i mi vlaptin"? *Medicina*, *57*(3), 1–22; Hanney, S. R., Wooding, S., Sussex, J., & Grant, J. (2020). From COVID-19 research to vaccine application: Why might it take 17 months not 17 years and what are the wider lessons? *Health Research Policy and Systems*, *18*(1), 1–10.

[16]Sharma, O., et al., op. cit. note 14.

[17]Idid.; Grady, C., Shah, S., Miller, F., Danis, M., Nicolini, M., Ochoa, J., Taylor, H., Wendler, D., & Rid, A. (2020). So much at stake: Ethical tradeoffs in accelerating SARSCoV-2 vaccine development. *Vaccine*, *38*(41), 6381–6387; Kashte, S., Gulbake, A., El-Amin, Iii, S. F., & Gupta, A. (2021). COVID-19 vaccines: Rapid development, implications, challenges and future prospects. *Human Cell*, *34*(3), 711–733; Lurie, N., Saville, M., Hatchett, R., & Halton, J. (2020). Developing COVID-19 vaccines at pandemic speed. *New England Journal of Medicine*, *31*(1), 1969–1973.

[18]Le, T. T., Andreadakis, Z., Kumar, A., Román, R. G., Tollefsen, S., Saville, M., & Mayhew, S. (2020). The COVID-19 vaccine development landscape. *Nature Reviews Drug Discovery*, *19*(May), 305–306.

[19]Pardi, N., et al., op. cit. note 11.

[20]Ibid.

[21]Arunachalam, M. A., Halwai, A., & Arunachalam, C. (2021). National guidelines for ethics committees reviewing biomedical & health research during COVID-19 pandemic: An analysis. *Indian Journal of Medical Ethics*, *VI*(1), 1–12.

[22]Bloom, D. E., et al., op cit. note 13.

play a crucial role,[23] and this was all the more evident in the case of COVID-19 vaccines: States committed from the very beginning to allocating massive financial resources to vaccine R&D, allowing research to proceed at a very high pace and trial phases to be conducted even in parallel. (Mostly public) funding was then streamlined and channeled through *ad hoc* financial mechanisms.[24] These include Advanced Purchase Commitments (APCs) by the European Commission, which entailed substantial down-payments to vaccine purchases in order to cover the up-front development costs and speed up the process,[25] and Operation Warp Speed (OWS), which was launched by the U.S. government to financially support the development of eight promising vaccines, enabling companies to scale up manufacturing when vaccines were still in early stages of clinical trials.[26] Ultimately, it could be argued that public funding represented a crucial pre-condition enabling the fast development of vaccines.

3.2 | Approval process

In Europe, medicinal products (including vaccines) are reviewed by EMA. After being technically validated, applications are assessed by the Committee for Medicinal Products for Human Use (CHMP), which, when necessary, is supported by other EMA Committees such as the Pharmacovigilance Risk Assessment Committee (PRAC) or the Committee on Advanced Therapies (CAT).[27] This evaluation can last up to 210 days and eventually results in a scientific opinion issued by the CHMP, addressing whether or not the vaccine may be authorized for use. Based on a CHMP positive opinion, and within 67 days, the European Commission takes the legally binding decision to authorize the vaccine, by granting an official Marketing Authorization, valid in all EU Member States.[28] In the case of emergency situations, however, such a long procedure is waived. In its place, specific procedural and regulatory tools are employed, such as the so-called "rolling reviews" and the issuance of Conditional Marketing Authorizations (CMAs). In addition, for COVID-19 vaccines' evaluation and approval, a dedicated task force, the COVID-19 EMA pandemic Task Force (COVID-ETF), was created, with the role of supporting EMA's scientific committees (CHMP and PRAC) and enabling EU Member States and the EU Commission to take quick and coordinate regulatory actions.

3.2.1 | Rolling reviews

A rolling review entails the evaluation of sets of data while trials are still ongoing. Through this approach, manufacturers did not have to provide the entire data and documentation for the evaluation process to begin but could start submitting data as soon as it was ready. There can be several rolling review cycles, with each cycle normally requiring a two-week review, depending on the amount of data. This procedural approach was of significant use, in particular for technology platforms which were already under development, because regulators could start to assess platforms while the COVID-19-specific data were still being generated.[29]

3.2.2 | CMAs

A CMA is an authorization specifically designed to expedite medical product licensure and to allow early marketing when their immediate availability has an important public-health impact.[30] In the past, CMAs have been granted to a variety of medicines, particularly to those addressing emergency situations linked to infectious diseases (i.e., Pandemic influenza vaccine H5N1 MedImmune), those targeting debilitating or life-threatening conditions (i.e., Votrient/pazopanib, used for the treatment of advanced Renal Cell Carcinoma), and those referred to as orphan medicines (i.e., Translarna/ataluren, used for the treatment of Duchenne muscular dystrophy).

A CMA can be granted only 3 days following a positive recommendation from EMA, and it allows to bring forward an authorization as soon as sufficient data have been gathered to demonstrate a positive risk–benefit ratio. Once a vaccine has obtained a CMA, however, a number of post-approval obligations legally apply. Additional post-marketing data must be provided within defined timelines, and EMA scientific committees carry out pharmacovigilance and manufacturing controls through evaluations on a continuous basis. CMAs are valid for 1 year and can be renewed annually or converted into standard Marketing Authorizations once the holder fulfills the obligations imposed and the complete data confirm the medicine's safety and efficacy.

All of the four COVID-19 vaccines under discussion were approved via this accelerated procedure.

4 | REVIEWING ETHICAL IMPLICATIONS

After tracing the key factors underpinning the development and approval of COVID-19 vaccines, a traditional review of ethical issues was performed. The review was aimed at identifying, mapping, and discussing the main ethical issues raised by the COVID-19 vaccine

[23]Mazzucato, M. (2013). *The Entrepreneurial State: Debunking public vs. private sector myths*. Anthem Press.
[24]Hanney, S. R., et al., op. cit. note 15.
[25]Bloom, D. E., et al., op cit. note 13.
[26]Slaoui, M., & Hepburn, M. (2020). Developing safe and effective covid vaccines—Operation warp speed's strategy and approach. *New England Journal of Medicine*, *383*(20), 1920–1931.
[27]Wagner, R., Meißner, J., Grabski, E., Sun, Y., Vieths, S., & Hildt, E. (2021). Regulatory concepts to guide and promote the accelerated but safe clinical development and licensure of COVID-19 vaccines in Europe. *Allergy*, *77*(1), 72–82.
[28]European Medicines Agency (EMA). *Obtaining an EU marketing authorisation, step-by-step*. Retrieved April 12, 2022, from https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step
[29]Wagner, R., et al., op. cit. note 27.
[30]European Commission (EC). (2020). *Questions and answers: Conditional marketing authorisation of COVID-19 vaccines in the EU*. Retrieved April 12, 2022, from https://ec.europa.eu/commission/presscorner/detail/en/qanda_20_2390

development and approval process while probing how the fast-tracking of such a process within an emergency situation impacted the basic ethical tenets of clinical research.

4.1 | Methods

4.1.1 | Search strategy

The onset of the SARS-CoV-2 pandemic has led to a wealth of COVID-19-related papers. Therefore, search strings had to be narrowed down in order to include only papers focusing on vaccines and vaccine-related ethical issues. The strings were built combining the following terms and keywords: "covid," "sars-cov-2," "vaccine," "ethics," "accelerated development." MeSH terms such as "ethical issue" were also used. The complete strings used are provided in Supporting Information: Appendix 2.

The database search was performed on July 16, 2021. Two different databases were queried: PubMed and Scopus, in order to cover the fields of healthcare sciences and bioethics. Language restriction was applied to the results, thus excluding studies not available in English or Italian. Articles published in scientific journals were taken into consideration without limitation as to their typology (e.g., original articles, reviews, commentaries, case reports, editorials, and letters to the editor were equally considered).

A total of 324 papers were retrieved through the queries. All the available texts were downloaded and managed with Mendeley Reference Manager. As to the screening process, after excluding duplicates (153), titles and abstracts of the remaining records (171) were screened to select the most relevant ones, in line with predefined inclusion and exclusion criteria (see below). Seventy-two papers were selected and a screening of the full text was performed. After the reading, a further 35 papers not meeting inclusion criteria were excluded.[31] A total of 37 articles were included. Bibliographies of relevant papers were examined and 18 additional papers that met the inclusion criteria were retrieved through manual searching and included. Finally, a total of 55 records were included in the review process. The full process of selection is reported in the flow chart in Figure 1, and a complete list of the records included in the review is provided in Supporting Information: Appendix 3.

4.1.2 | Inclusion criteria

Publications were included on the basis of the following conditions: (i) addressing issues related to the accelerated R&D and approval phases of vaccine development and (ii) tackling implications for the four vaccines approved in the EU.

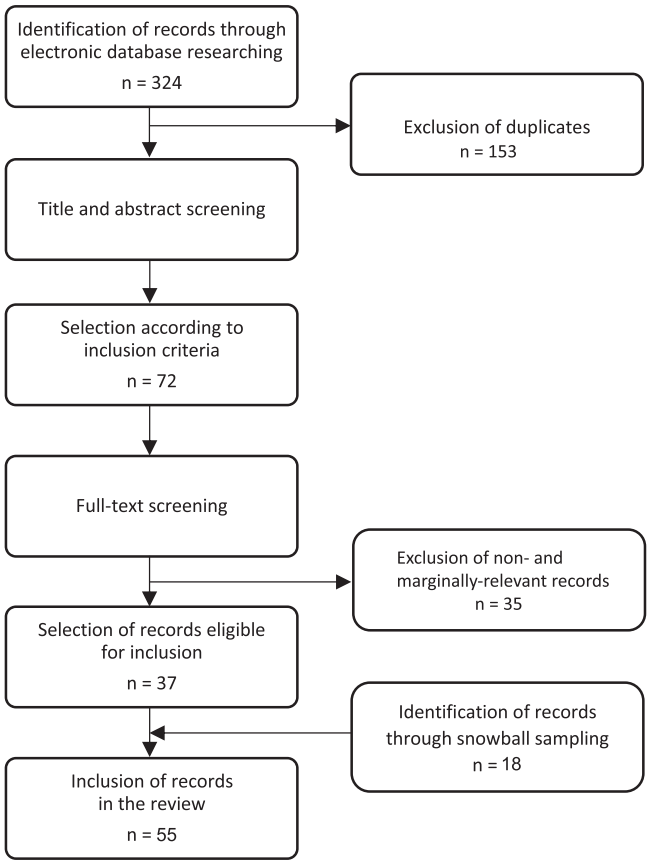

FIGURE 1 Flowchart showing the electronic database search and record selection procedure.

4.1.3 | Exclusion criteria

The following types of publications were excluded from the review: (i) papers referring to diagnostic tools or experimental treatments for COVID-19 other than vaccines (i.e., antiviral medicines and medical devices), (ii) papers addressing issues in the administration or allocation of vaccines, and (iii) papers focusing exclusively on vaccines authorized outside the EU or issues not related to the European context.

4.1.4 | Results

The most relevant ethical issues arisen from the review were classified into four main subgroups, which will be tackled in the next section in the following order:

1. Safety concerns resulting from the acceleration of the R&D process and the use of new technologies (addressed in 24 papers).

[31] Among these were papers deemed only marginally relevant to the topic discussed. Authors considered as marginally relevant those papers discussing ethical issues not strictly related to the acceleration of the R&D and approval process. An example of excluded papers is "Zimmerman, R. K. (2021). Helping patients with ethical concerns about COVID-19 vaccines in light of fetal cell lines used in some COVID-19 vaccines. *Vaccine*, *39*(31), 4242–4244," because, despite discussing a relevant ethical issue, it is not directly related to the fast-tracking of the development process, and therefore not at the core of our analysis.

2. Issues related to the early licensing of vaccines and the ensuing impact on the design of trials (26 papers).
3. Challenges posed by the enrollment of study participants (24 papers).
4. Issues regarding informed consent (11 papers).

4.2 | Safety concerns

Before the outbreak of the SARS-CoV-2 pandemic, speeding up the development and evaluation of candidate drugs was already relatively commonplace. CMAs first started to be used in 2006 to provide expedited routes for EMA authorization[32]; during vaccine trials (i.e., for Ervebo), researchers enrolled participants in a trial phase before published data on the previous phase were available,[33] and surrogate endpoints (intermediate endpoints intended to substitute for and predict a clinical outcome), even nonvalidated ones, were often used in clinical trials to reduce drug development time.[34]

Nevertheless, the development and approval of a vaccine had never been fast-tracked to this extent, leading to concerns that, by deviating from standard procedures, and potentially exposing individuals to an investigational vaccine while safety is still being assessed, the health of both research participants and the future vaccinees could be put at risk.[35]

4.2.1 | Lack of animal testing

When scientists first began researching candidate vaccines, the animal disease models for SARS-CoV-2 were still under study, so their efficiency and their ability to mimic human pathogenesis were uncertain. Therefore, Moderna and other biotech companies overlapped preclinical studies with Phase 1 human trials and started testing the safety and toxicity of their vaccines simultaneously in animals and in humans.[36] This decision was highly contested, though NIAID, conducting the trials, claimed that in a situation of the pandemic "the risk of delaying the advancement of vaccines was much higher than the risk of causing illness in healthy volunteers."[37]

Since research participants were confronting a very high risk of disease, the potential benefits were deemed to justify greater risks in research design, so animal testing was skipped and the timeline was greatly hastened.

4.2.2 | Lack of time to identify possible side effects

As COVID-19 vaccines underwent compressed clinical trial timeframes, less time was available to identify possible side effects, which might emerge in the long run.[38] As a consequence, when vaccines are administered to the general population, safety-related concerns persist. In this situation, the only way to mitigate the risks and provide an ethical justification for the early deployment of vaccines is by implementing a very careful post-marketing safety monitoring plan.

For this purpose, in Europe, before starting the extensive vaccination campaigns, EMA and the national competent authorities developed a detailed pharmacovigilance plan outlining all the monitoring activities to be carried out after the marketing of the vaccines.[39] On a monthly basis, Marketing Authorization Holders are expected to submit summary safety reports (MSSRs) to EMA; ongoing clinical trials and new observational studies continue to provide results and updated safety data; and at any time, unusual or unexpected reactions to the vaccine are to be reported by individuals or healthcare professionals in the EudraVigilance database. EMA's PRAC is charged with reviewing these reports and data, as well as medical literature and data from clinical and epidemiological studies, in order to identify any potential risks to the health of vaccine recipients. On a regular basis, EMA publishes a safety update on each authorized vaccine, providing information on newly observed side effects, as well as warnings and recommendations.

4.2.3 | Risks related to new technologies

COVID-19 vaccines rely on mRNA- and DNA-based platforms. These new technologies have not been extensively tested yet, so their characteristics are to some extent still unscrutinized. During the development of COVID-19 vaccines, several concerns about mRNA- and DNA-based vaccines have been raised. One of the most relevant and discussed issue was that mRNA vaccines could generate inflammation and lead to autoimmune conditions, especially in genetically predisposed subjects.[40] However, the risk assumption was based on a theoretical framework, and calls have been made for

[32]EMA. (2017). *Conditional marketing authorisation. Report on ten years of experience at the European Medicines Agency* Retrieved April 12, 2022, from https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf; Pinilla-Dominguez, P., Naci, H., Osipenko, L., & Mossialos, E. (2020). NICE's evaluations of medicines authorized by EMA with conditional marketing authorization or under exceptional circumstances. *International Journal of Technology Assessment in Health Care*, *36*(4), 1–8.

[33]Smith, M. J., Emanuel, E. J., Thomé, B., & Upshur. R. E. G. (2021). Ethical conditions for accelerating COVID-19 vaccine research. *Wellcome Open Research*, *5*, 1–7.

[34]Bruce, C. S., Brhlikova, P., Heath, J., & McGettigan, P. (2019). The use of validated and nonvalidated surrogate endpoints in two European Medicines Agency expedited approval pathways: A cross-sectional study of products authorised 2011-2018. *PLoS Medicine*, *16*(9), e1002873.

[35]Smith, M. J., et al., op. cit. note 33; Komesaroff, P. A. (2020). Ethical challenges posed by COVID-19. *Respirology*, *25*(10), 1035–1036.

[36]Deb, B., Shah, H., & Goel, S. (2020). Current global vaccine and drug efforts against COVID-19: Pros and cons of bypassing animal trials. *Journal of Biosciences*, *45*(1), 82.

[37]Hanney, S. R., et al., op. cit. note 15.

[38]Bloom, D. E., et al., op cit. note 13.

[39]EMA. (2020). *Pharmacovigilance plan of the EU regulatory network for COVID-19 vaccines*. Retrieved April 12, 2022, from https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-COVID-19-vaccines_en.pdf

[40]Talotta, R. (2021). Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases." *Clinical Immunology*, *224*, *108665*; Wibawa, T. (2021). COVID-19 vaccine research and development: ethical issues. *Tropical Medicine and International Health*, *26*(1), 14–19.

conducting more extensive studies to better estimate the autoimmune-inducing capability of SARS-CoV-2 antigens[41]. As vaccines were being administered to the general population, the importance of post-marketing pharmacovigilance had to be stressed, as it allowed to proceed with due caution even in light of an accelerated R&D and approval process.

4.3 | Issues in early licensing and study design

The design of COVID-19 vaccine trials was geared to fast-track the R&D process and, in turn, raised the following set of issues.

4.3.1 | Unblinding trials

The first major issue related to study design is the difficulty in the acquisition of long-term data. This owed not only to the short duration of trials but also to the early deployment of vaccines, which interfered with the acquisition of long-term data.[42]

According to the international ethical and scientific standard for conducting clinical research enshrined in the Good Clinical Practice guidelines, subjects involved in a study should be "informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial."[43] Therefore, in a blinded trial, once a vaccine proves to be effective and starts to be available, researchers have an ethical obligation to unblind the two study arms, in order to provide participants with the option to seek the vaccine outside the trial, upon meeting the eligibility criteria for the priority groups of vaccination.[44] Moreover, in order to prevent trial drop-outs, some companies offered vaccination to participants in the placebo arm.[45] Inevitably, this was detrimental to the ongoing trials, hindering the long-term comparison of the vaccine to the placebo.[46] However, vaccinating the placebo arm and adjusting to an open-label study allowed, at least, the collection of some additional data on longer-term safety and efficacy.[47] This was considered the best option to benefit, at the same time, the individuals enrolled in the trials and the general population while catering to both the principles of beneficence and justice.[48]

4.3.2 | Evaluation of new candidate vaccines: use of the placebo and alternative study designs

The early granting of a CMA to a vaccine also complicates the evaluation of new candidate vaccines. One of the most discussed aspects of this issue is the use of the placebo as a control in clinical trials following the authorization of an effective vaccine. According to the Declaration of Helsinki (2013) and to the CIOMS Guidelines (2016), the use of the placebo in the control arm of a trial is ethically acceptable only "when no proven intervention exists."[49] When trials for COVID-19 vaccines first started, a state of clinical equipoise existed, as the therapeutic validity of the intervention under study had yet to be ascertained[50]; therefore, investigators could randomly assign participants to a placebo or intervention group. Since the first vaccine was found to be safe and efficacious, though, in countries where such temporarily authorized vaccine was available (such as European ones),[51] placebo-controlled trials could no longer be considered acceptable.[52]

In response to this challenging ethical issue, the WHO published a policy brief, which stated that: "A candidate vaccine's attainment of emergency use designation does not, in itself, render that candidate the best proven intervention […] Accordingly, the continued use of placebos or active controls in the control arm of current or future trials testing other candidate vaccines […] should not be regarded as violating the Declaration of Helsinki, CIOMS, or WHO's previous guidance."[53] This policy brief further emphasized that the use of a placebo control can be justified by the social value of the research,[54] and therefore legitimized the conduct of blinded, placebo-controlled

[41]Vojdani, A., & Kharrazian, D. (2020). Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. *Clinical Immunology*, *217*, 108480; Vojdani, A., Vojdani, E., & Kharrazian, D. (2021). Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: Implications for autoimmune diseases. *Frontiers in Immunology*, *11*, *617089*.

[42]Dal-Ré, R., Caplan, A. L., Gluud, C., & Porcher, R. (2021). Ethical and scientific considerations regarding the early approval and deployment of a COVID-19 vaccine. *Annals of Internal Medicine*, *174*(2), 258–260.

[43]WHO. (2002). *Handbook for good clinical research practice (GCP) guidance for implementation*.

[44]Dal-Ré, R., et al., op. cit. note 42; Ravinetto, R. (2021). Problematic COVID-19 vaccine trials in times of vaccine nationalism. *Indian Journal of Medical Ethics*, *VI*(2), 1–7; Wendler, D. et al. (2020). COVID-19 vaccine trial ethics once we have efficacious vaccines. *Science*, *370*(6522), 1277–1279.

[45]ClinicalTrials.gov. (2020). A study to evaluate efficacy, safety, and immunogenicity of mRNA-1273 vaccine in adults aged 18 years and older to prevent COVID-19. Retrieved April 12, 2022 from https://clinicaltrials.gov/ct2/show/NCT04470427; Eyal, N., & Lipsitch, M. (2021). How to test severe acute respiratory syndrome coronavirus 2 vaccines ethically even after one is available. *Clinical Infectious Diseases*, *VI*(2), 128–129.

[46]Haire, B. (2021). The continued use of placebo arms in COVID-19 vaccine trials does not adequately protect the well-being of participants. *Indian Journal of Medical Ethics*, *6*(2), 1–10.

[47]Cash, R. A. (2021). Testing vaccines in the time of Covid: The changing landscape. *Indian Journal of Medical Ethics*, *VI*(2), 1–4.

[48]Stoehr, J. R., Hamidian Jahromi, A., & Thomason, C. (2021). Ethical considerations for unblinding and vaccinating COVID-19 vaccine trial placebo group participants. *Frontiers in Public Health*, *9*, 702960.

[49]World Medical Association. (2013). *DECLARATION OF HELSINKI—Ethical principles for medical research involving human subjects*; Greco, D. B. (2021). Ethical limits to placebo use and access to COVID-19 vaccines as a human right. *Indian Journal of Medical Ethics*, *VI*(2), 1–14; Greco, D. B. (2021). Ethical limits to placebo use and access to COVID-19 vaccines as a human right. *Indian Journal of Medical Ethics*, *VI*(2), 1–14.

[50]Dal-Rè, R. (2021). Clinical equipoise in COVID-19 vaccine candidate trials. *The Journal of Clinical Pharmacology*, *61*(9), 1249–1250.

[51]Dal-Ré, R. (2022) Placebo control group in COVID-19 vaccine trials: context and timing matters. *European Journal of Clinical Pharmacology*, *78*, 523–526.

[52]Dal-Ré, R., et al., op. cit. note 42; Ravinetto, op. cit. note 59; Wendler et al., op. cit. note 60; Friesen, P., Caplan, A. L., & Miller, J. E. (2021). COVID-19 vaccine research and the trouble with clinical equipoise. *The Lancet*, *397*(10274), 576.

[53]WHO. (2020). *Emergency use designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding*. Retrieved April 12, 2022, from https://apps.who.int/iris/handle/10665/337940

[54]Brüssow, H. (2021). COVID-19: Vaccination problems. *Environmental Microbiology*, *23*(6), 2878–2890; Eckstein, L., Rid, A., Kamuya, D., & Shah, S. K. (2021). The essential role of Data and Safety Monitoring Boards (DSMBs) in ensuring the ethics of global vaccine trials to address coronavirus disease 2019 (COVID-19). *Clinical Infectious Diseases*, *73*(11), 2126–2130.

vaccine trials even in the context of a candidate vaccine being publicly accessible.

Nevertheless, many have argued that once all individuals 18 years and older become eligible for vaccination, alternative approaches must start to be considered, such as *non-inferiority trials*, where a candidate vaccine is compared to an already authorized vaccine, to demonstrate that the new vaccine is no worse than the comparator,[55] or *controlled human infection (CHI) trials*, where a candidate vaccine, after going through phase I safety and dosage trials, is administered to volunteers, who are then deliberately infected with the virus, in order to see how well the vaccine protects them.[56]

While these study designs would provide a valuable solution to the placebo-related issues, they also give rise to different kinds of ethical issues. For instance, in the case of CHI, a problematic risk–benefit ratio generates by exposing healthy volunteers to SARS-CoV-2 at a time when a cure for COVID-19 was not available yet.[57]

4.4 | Issues in the enrollment of participants

Two other ethically challenging aspects revolved around the enrollment of participant populations in clinical studies.

4.4.1 | Under-represented populations

In a situation of the pandemic, any developed vaccine is, by definition, intended for administration to the global population. Yet, the study population is comparatively much smaller and does not optimally represent the diversity of the intended target population. This issue is exacerbated by COVID-19 vaccines' fast-tracked trials, whose reduced sample size made it even more difficult to take all demographic groups into appropriate consideration, hindering the generalizability of the resulting safety and efficacy data, with under-represented groups being the ones more exposed to unexpected harms.[58]

To compensate for this issue, from a justice-based perspective, the enrollment should target populations who are most likely to benefit from the candidate vaccine. In the case of COVID-19 vaccines, these include groups at the highest risk for infection, serious morbidity or mortality, namely, older adults, as well as socio-economically deprived populations, including ethnic minorities.[59] However, it has been pointed out that the majority of COVID-19 vaccine trials have missed the target, as both these groups were under-represented. Older adults were often excluded from the enrollment in trials, either directly, with an upper age limit, or through other indirect selection criteria.[60] Similarly, the percentage of ethnic minority participants involved in COVID-19 vaccine trials was very low, due to a variety of reasons, including longstanding mistrust in public health governance systems and socio-cultural barriers.[61]

In addition, insofar as participants' enrollment rate has been shown to be associated with vaccination rates within specific populations, an inequitable enrollment in clinical trials may be held responsible for the high prevalence of vaccine hesitancy across minority groups.[62]

4.4.2 | Enrollment of vulnerable populations in low- and middle-income countries (LMICs)

Epidemic outbreaks caused by novel pathogens often emerge, and are particularly devastating, in LMICs, characterized by a limited capacity of health systems and ensuing high rates of vulnerable subjects within the population. According to justice-based accounts of vulnerability,[63] the latter entails "facing a significant probability of incurring in harm during research—such as invalid consent or denied access to the benefits of research—while substantially lacking the ability or means to protect oneself."[64]

[55]Dal-Ré, R., Bekker, L.-G., Gluud, C., Holm, S., Jha, V., Poland, G. A., Rosendaal, F. R., Schwarzer-Daum, B., Sevene, E., Tinto, H., Voo, T. C., & Sreeharan, N. (2021). Ongoing and future COVID-19 vaccine clinical trials: Challenges and opportunities. *The Lancet Infectious Diseases*, *21*(11), E342–E347; Fleming, T. R., Krause, P. R., Nason, M., Longini, I. M., & Henao-Restrepo, A.-M. M.(2021). COVID-19 vaccine trials: The use of active controls and non-inferiority studies. *Clinical Trials*, *18*(3), 335–342.

[56]Dal-Ré, R., et al., op. cit. note 55; Jamrozik, E., Heriot, G. S., & Selgelid, M. J. (2020). Coronavirus human infection challenge studies: Assessing potential benefits and risks. *Journal of Bioethical Inquiry*, *17*(4), 709–715; Schaefer, G. O., Tam, C. C., Savulescu, J., & Voo, T. C. (2020). COVID-19 vaccine development: Time to consider SARS-CoV-2 challenge studies? *Vaccine*, *38*(33), 5085–5088.

[57]Richards, A. D. (2020). Ethical guidelines for deliberately infecting volunteers with COVID-19. *Journal of Medical Ethics*, *46*(8), 502–504.

[58]Sharma, O., et al., op. cit. note 14; Flores, L. E., Frontera, W. R., Andrasik, M. P., Del Rio, C., Mondríguez-González, A., Price, S. A., Krantz, E. M., Pergam, S. A., & Silver, J. K. (2021). Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Network Open*, *4*(2), e2037640; Ogbogu, U. & Hardcastle, L. (2020). Bioethics and practical justice in the post-COVID-19 era. *Developing World Bioethics*, *21*(1), 31–35; Pepperrell, T., Rodgers, F., Tandon, P., Sarsfield, K., Pugh-Jones, M., Rashid, T., & Keestra, S. (2021). Making a COVID-19 vaccine that works for everyone: Ensuring equity and inclusivity in clinical trials. *Global Health Action*, *14*(1), 1892309.

[59]Mackey, K. et al. (2021). Racial and ethnic disparities in COVID-19-related infections, hospitalizations, and deaths: A systematic review. *Annals of Internal Medicine*, *174*(3), 362–373.

[60]Helfand, B. K. I., Webb, M., & Gartaganis, S. L. (2020). The exclusion of older persons from vaccine and treatment trials for coronavirus disease 2019—Missing the target. *JAMA Internal Medicine*, *180*(11), 1546–1549; Prendki, V., Tau, N., Avni, T., Falcone, M., Huttner, A., Kaiser, L., Paul, M., Leibovici-Weissmann, Y., Yahav, D., & ESCMID Study Group for Infections in the Elderly (ESGIE). (2020). A systematic review assessing the under-representation of elderly adults in COVID-19 trials. *BMC Geriatrics*, *20*(1), 538; Veronese, N., Petrovic, M., Benetos, A., Denkinger, M., Gudmundsson, A., Knol, W., Marking, C., Soulis, G., Maggi, S., Cherubini, A., & special interest group in Systematic Reviews and Meta-analyses and the task force on Pharmaceutical strategy of the European Geriatric Medicine Society (EuGMS). (2021). Underrepresentation of older adults in clinical trials on COVID-19 vaccines: A systematic review. *Ageing Research Reviews*, *71*, *101455*.

[61]Etti, M., Fofie, H., Razai, M., Crawshaw, A. F., Hargreaves, S., & Goldsmith, L. P. (2021). Ethnic minority and migrant underrepresentation in COVID-19 research: Causes and solutions. *EClinicalMedicine*, *36*, 100903; NIHR. (2020). *NIHR research ethnicity data provides insight on participation in COVID-19 studies*. Retrieved April 12, 2022, from https://www.nihr.ac.uk/news/nihr-research-ethnicity-data-provides-insight-on-participation-in-COVID-19-studies/26460

[62]Flores, L. E., et al., op. cit. note 58.

[63]ten Have, H. (2015). Respect for human vulnerability: The emergence of a new principle in bioethics. *Journal of Bioethical Inquiry*, *12*(3), 395–408.

[64]Monrad, J. T. (2020). Ethical considerations for epidemic vaccine trials. *Journal of Medical Ethics*, *46*(7), 465–469; Schroeder, D., & Gefenas, E. (2009). Vulnerability: Too vague and too broad? *Cambridge Quarterly of Healthcare Ethics*, *18*(2), 113–121.

COVID-19 vaccine trials were, at first, largely conducted in developed nations, with enrolled participants representative of high-income settings and the exclusion of ethnicities, which were most affected by COVID-19 globally.[65] However, once vaccines started to be available in economically developed countries, and enrolling participants to test new candidate vaccines became increasingly difficult, researchers started considering countries with limited or no access to authorized vaccines as potential locations to continue the trials. While this could broaden the sample population, a lurking risk of exploitation existed. Indeed, to avoid exploitation, researchers are required to comply with the basic ethical principle of justice, which, in its classic formulation, provides that "research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research."[66] In other terms, host communities should be able to benefit from the results of the trials, by eventually having access to the vaccine that was tested on them.[67] Since the start of the pandemic, initiatives such as COVAX have been launched to guarantee a fair and equitable access to vaccines in every country of the world.[68] In particular, the Gavi COVAX Advance Market Commitment (AMC) was created to ensure that 92 LMICs, that cannot fully afford to pay for COVID-19 vaccines, would get equal access to vaccination.[69]

Yet, as of February 2022, with more than 10 billion vaccine doses administered worldwide, a stark gap still existed between vaccination programs in different parts of the world: according to The New York Times World Vaccination Tracker, while in upper–middle-income countries, the vaccination rate was at 78%, in low-income countries, only 11% of the population had received at least one dose. Therefore, the conduct of clinical trials in such countries appears highly questionable from an ethical standpoint.[70]

4.5 | Issues in the informed consent

Finally, issues arose around the ability of trial participants to provide fully valid informed consent, which, by definition, requires both effective information and uncoerced agreement to participate in the clinical trial.[71] While the provision of valid informed consent represents an 'old, yet unresolved issue' in clinical research,[72] inasmuch as a complete understanding of informed consent components represents all too often a still elusive requirement,[73] the contextual conditions underpinning R&D for COVID-19 vaccines appear to have exacerbated this issue.

For one thing, informed consent documents used in four phase 3 trials for COVID-19 vaccines have been shown to be too long, difficult to read, and characterized by exceedingly complex language. Moreover, most documents were lacking some fundamental information, such as the indication of what would happen to the placebo group in case other vaccines were proven safe and effective.[74] Moreover, with regards to the broader consent procedures, scant time was made available for face-to-face communication between the participant and investigator, as the latter had to fulfill the dual responsibility of treating patients and researching possible cures and vaccines in clinical trials[75]; in some cases, consent had to be obtained virtually.[76] In such a scenario, further characterized by the need to proceed with a swift enrollment of participants, too small emphasis was put on the informed consent procedure. This may have violated the principle of autonomy and the degree of information it requires.[77]

5 | DISCUSSION

This review of the published literature around the development and regulatory approvals of COVID-19 vaccines in the EU identified a set of issues that emerge as ethically challenging and revolve around safety, study design, enrollment of participants, and the acquisition of informed consent. As the review reveals, deviations from standard requirements occurred, to prioritize other aspects of research, such as rapidity. The notion that core methodological and ethical components of high-quality research are dispensable in an emergency situation has been criticized as not only morally flawed but also as conducive to suboptimal clinical outcomes and hence lesser value for individual patients and society as a whole.[78] Yet, while some aspects of COVID-19 vaccines' trials, namely those related to underrepresentation and vulnerability issues in the enrollment of

[65]Dal-Ré, R., et al., op. cit. note 55; Ogbogu & Hardcastle, op. cit. note 58.
[66]National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *THE BELMONT REPORT—Ethical principles and guidelines for the protection of human subjects of research*.
[67]Dal-Ré, R., et al., op. cit. note 55; Dawson, A., Emanuel, E. J., Parker, M., Smith, M. J., & Voo, T. C. (2020). Key ethical concepts and their application to COVID-19 research. *Public Health Ethics*, *13*(2), 127–132.
[68]Ogbogu & Hardcastle, op. cit. note 58; Kim, J. H., Hotez, P., Batista, C., Ergonul, O., Figueroa, J. P., Gilbert, S., Gursel, M., Hassanain, M., Kang, G., Lall, B., Larson, H., Naniche, D., Sheahan, T., Shoham, S., Wilder-Smith, A., Strub-Wourgaft, N., Yadav, P., & Bottazzi, M. E. (2021). Operation Warp Speed: Implications for global vaccine security. *The Lancet Global Health*, *9*(7), e1017–e1021.
[69]Perera, P.-Y., & Perera, L. P. (2021). Development of leading first-generation vaccines against SARS-CoV-2. *Microbes and Infection*, *23*(8), 104841; Simoneaux, R., & Shafer, S. L. (2020). Update on COVID-19 vaccine development. *ASA Monitor*, *84*(8), 17–18.
[70]Ogbogu & Hardcastle, op. cit. note 58.
[71]World Medical Association, op. cit. note 49; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, op. cit. note 66.
[72]Sanchini, V., Reni, M., Calori, G., Riva, E., & Reichlin, M. (2014). Informed consent as an ethical requirement in clinical trials: An old, but still unresolved issue. An observational study to evaluate patient's informed consent comprehension. *Journal of Medical Ethics*, *40*(4), 269–275.
[73]Tam, N. T., Huy, N. T., Thoa, L. T. B., Long, N. P., Trang, N. T. H., Hirayama, K., & eKarbwang, J. (2015). Participants' understanding of informed consent in clinical trials over three decades: Systematic review and meta-analysis. *Bulletin of the World Health Organization*, *93*(3), 186–198.
[74]Emanuel, E. J., Osterholm, M., & Gounder, C. R. (2021). Assessment of length and readability of informed consent documents for COVID-19 vaccine trials. *JAMA Network Open*, *4*(4), e2110843.
[75]Jones, X. M., Zimba, O., & Gupta, L. (2021). Informed consent for scholarly articles during the COVID-19 pandemic. *Journal of Korean Medical Science*, *36*(2), 1–9.
[76]Gamad, N., Shafiq, N., Mohindra, R., Bhalla, A., & Malhotra, S. (2022). Some reflections on vaccine research ethics during COVID-19 pandemic. *Postgraduate Medical Journal*, *98*(e2), e84–e85. Hashem, H., Abufaraj, M., Tbakhi, A., & Sultan, I. (2020). Obstacles and considerations related to clinical trial research during the COVID-19 pandemic. *Frontiers in Medicine*, *7*, *598038*.
[77]Dawson, A., et al., op. cit. note 67; Jones, X. M., et al., op. cit. note 75.
[78]London. A. J., & Kimmelman, J. (2020). Against pandemic research exceptionalism. *Science*, *368*(6490), 476–477.

participants, as well as informed consent provision, could be said to have remained, in part, ethically unaddressed, for some others ethical justifications were provided.

Notably, waivers to standard procedures, such as the lower amount of (long-term) data provided, and used by EMA to grant an authorization, were (and could be) deemed ethically acceptable only on the basis of the implementation of robust pharmacovigilance (phase 4) programs, once vaccines start to be administered to the population. Accordingly, pharmacovigilance represents the ethical as well as regulatory pivot of the vaccination R&D and regulatory approval processes, geared to minimize individual harms and maximize benefits to individual people and society at large. Conversely, shortcomings in (European as well as national) pharmacovigilance plans, such as lack of active alongside passive surveillance and under-reporting of adverse reactions, would undermine the ethical acceptability of the whole fast-tracked process. Ethical issues potentially raised by sub-optimal pharmacovigilance implementation in European nations thus deserve further empirically-informed scrutiny.

6 | CONCLUSION

The advent of COVID-19 vaccines has had a major impact on the evolution of the pandemic worldwide. In this article, we scrutinized the main factors impinging on the accelerated R&D and regulatory approval of the first four COVID-19 vaccines authorized in Europe by EMA. With a review of published literature, we further traced and discussed the key ethical implications of such a process. The article provides a nuanced perspective, devoid of dichotomic and largely simplistic framings all too often proliferating in the public discourse, around key steps and criticalities in the R&D and regulatory approval processes, which is ultimately intended to inform policy and public debates on such a crucial issue for our societies.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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