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PHARMACOVIGILANCE

The winding 12-month journey of the AstraZeneca COVID-19 vaccine since its first administration to humans

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Received 3 March 2022; accepted 7 July 2022
Available online 13 July 2022

KEYWORDS
AstraZeneca COVID-19 vaccine; ChAdOx1 nCoV-19; Clinical trials; Effectiveness; Efficacy; Safety; Thrombotic thrombocytopenia

Summary The deficiently designed and conducted initial clinical development plan and the occurrence of thrombotic thrombocytopenia cases, have marked the first 12-month journey of the AstraZeneca coronavirus disease 2019 (COVID-19) vaccine after it was first administered to humans. When it was authorized, there were no available efficacy data in the elderly. However, this age group was included in the product labelling based on immunogenicity data. The lack of safety and efficacy data in the elderly that was acknowledged in the product information, triggered most European Union (EU) countries to limit the administration of this vaccine to certain age groups. In February-March/2021, after the results of observational studies supported the vaccine effectiveness in the elderly, several countries broadened its use to this age group. When trust on the vaccine was ramping up, unusual blood clot cases were described in Europe, which led 24 countries around the world to temporarily halt its administration. These cases were first described as thrombotic thrombocytopenia in late March. In mid-April, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) updated the product information and confirmed the positive benefit/risk ratio of the vaccine, recommending its use with no age restrictions. The World Health Organization (WHO) coincided with this approach. However, several countries decided to limit its use to certain age groups. The EMA listed thrombotic thrombocytopenia as a "very rare" adverse reaction. Although, the AstraZeneca vaccine was conceived in early 2020 to be a worldwide leader in the fight against COVID-19, its use was abandoned by the African Union, Denmark, and Israel. However, this vaccine has shown its usefulness in many settings across the world.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| CDC          | Centers for Disease Control and Prevention |
| CEO          | chief executive officer |
| COVAX        | COVID-19 Vaccines Global Access |
| EMA          | European Medicines Agency |
| EU           | European Union |
| FDA          | Food and Drug Administration |
| LD           | low dose |
| MERS-CoV     | Middle East respiratory syndrome coronavirus |
| MHRA         | Medicines and Healthcare products Regulatory Agency |
| NIAID        | National Institute of Allergy and Infectious Diseases |
| RCT          | randomized controlled trial |
| SARS-CoV-2   | severe acute respiratory syndrome coronavirus 2 |
| SD           | standard dose |
| UK           | United Kingdom |
| USA          | United States of America |
| WHO          | World Health Organization |

Introduction

The University of Oxford started to work on adenovirus vector vaccines in 2005. Based on pre-existing pre-clinical studies of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), this university started the clinical development of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2 in the spring of 2020. At the same time, the University of Oxford signed a contract with AstraZeneca to worldwide manufacturing and distributed the coronavirus disease 2019 (COVID-19) vaccine on a not-for-profit basis for the duration of the pandemic [1]. This vaccine must be stored at normal fridge temperature (2-8°C), enabling its use in any country. This was superb news for everyone, but especially for low- and middle-income countries that were desperately in need to vaccinate their populations, even though most of them were lacking the resources to do so, and for COVID-19 Vaccines Global Access (COVAX), a global initiative aimed at rapid, fair and equitable access to COVID-19 vaccines [2]. In August 2020, AstraZeneca was willing to deliver 300 million doses to COVAX by the end of 2021 [3]. In those days, Oxford/AstraZeneca generated sympathy and the highest expectations for becoming the most important COVID-19 vaccine worldwide. AstraZeneca announced its intention to supply to 142 countries and to become--through its partner Serum Institute of India--the biggest initial supplier to COVAX [4]. In April 2021, however, the picture was quite different and several countries had limited its use to certain population age groups. Therefore, it is worth looking back to review the most relevant events that occurred in the first 12 months after its first administration to humans. The clinical development of this vaccine, that has been anything but straightforward and clean, was the first critical event. It was accomplished by regulatory decisions made by the UK regulatory agency (MHRA) in an unusual problematic pandemic situation that marked the path to almost all other regulatory agencies [5] that ultimately impacted how the vaccine was rolled out in many countries. The description of unusual cases of thrombosis with thrombocytopenia—that led several European Union (EU) countries to temporarily stop its administration—was the second critical event that has stamped the perception of this vaccine across the world. This review is focused on the description and interpretation of the most relevant facts that occurred since April 2020 and that impacted the deployment of the AstraZeneca COVID-19 vaccine up to April 2021.

Most relevant facts in the pre-authorization period of the AstraZeneca COVID-19 vaccine (Supplemental material-1)

The clinical development of this vaccine candidate started on 23 April 2020 with a phase 1/2 randomized controlled trial (RCT) conducted in the UK. On those days, a few other sponsors were starting their first trials in humans. In the following two months, three additional trials in the UK (phase 2/3), Brazil (phase 3) and South Africa (phase 1/2) were also initiated. In late August, a large phase 3 RCT started recruitment in the USA. On 6 September, all trials were put on hold due to a suspected serious adverse event in a trial participant [6]; this was the second time all trials were paused for serious neurological safety reasons, after the first one in July [7]. In mid-September, trials conducted outside the USA were resumed [8–11]; the American trial resumed on 23 October [12].

Amid huge pressure from President Trump on having a vaccine available by early November [13], CEOs of AstraZeneca and other eight biopharma companies issued on 8 September a public statement to ensure public confidence that they will “uphold the integrity of the scientific process” [14]. These companies pledged to submit for approval or emergency use authorization only after positive results were obtained in a phase 3 RCT [14].

Interim results of randomized controlled trials published

The interim results of the four RCTs conducted in the UK, Brazil and South Africa were published on 8 December. The pre-specified global statistical plan was agreed with the MHRA [15]. Since this was “signed off before any data analysis was conducted” [15], this should have happened, at best, only a few weeks after the aforementioned AstraZeneca’s chief executive officer (CEO) public commitment. The increasing concerns on the pandemic indicators in the UK and the delay in resuming the phase 3 in the USA might have influenced the decision of using the results of these four RCTs in the UK regulatory process.

Voysey et al. [15] reported four facts that, up to now, have not happened in the development of any other COVID-19 vaccine candidate that were temporarily authorized in western countries and by the World Health organization (WHO) [i.e., Janssen, Moderna, Novavax and Pfizer/BioNTech]. First, the analysis to assess the vaccine efficacy included pooled data from two RCTs—conducted in the UK and Brazil. Second, in the UK trial, due to
manufacturing problems, two different vaccine doses were administered as a priming dose [low dose (LD), or standard dose (SD)]. All participants received the SD as booster dose. In the trial run in Brazil all participants received two SD doses. The LD+SD regimen provided higher vaccine efficacy (90%) than the SD+SD regimen (62%). Third, since both trials were designed as single-dose RCTs, the time elapsed between the priming dose and the booster dose varied considerably. And fourth, the vaccine efficacy in older age groups (≥56-year-olds) could not be assessed due to a limited number of participants and COVID-19 cases (Supplemental material-2 provides the summary of trial results).

Emergency supply granted in the UK

On 30 December 2020, four days after the new SARS-CoV-2 variant (B.1.1.7), that was spreading in the UK, was found to be more transmissible [16], the MHRA granted emergency supply [17] based on the same RCTs described by Voysey et al. The MHRA, likely forced by a surge on COVID-19 cases, the growing prominence of a new variant (B.1.1.7) and the shortfall of vaccines (only the Pfizer/BioNTech was available in December 2020), authorized the AstraZeneca vaccine to prevent COVID-19 in ≥18-year-old individuals [5]; two SD doses should be given 4–12 months apart—as advised by the UK Joint Committee on Vaccination and Immunisation [18]. Exploratory analyses showed that immunogenicity increased with a longer dosing interval. The 12-week limit, however, was chosen likely for convenience since there were no immunogenicity or vaccine efficacy data available at this specific time point [17]. No vaccine efficacy data could be estimated for the elderly, due to the small group (n = 660) and COVID-19 cases (n = 2). The MHRA concluded that both efficacy and safety data were limited in 65-year-old individuals [17]. Argentina authorized the vaccine the very same day as the UK [19]. In a few days, several countries (e.g., Bangladesh, India, Mexico, Pakistan, South Africa and Thailand) did the same.

Most relevant facts of the post-authorization journey of the AstraZeneca COVID-19 vaccine (Supplemental material-3)

The EMA recommended conditional marketing authorization to the European Commission on 29 January 2021. The EMA, after assessing the same RCTs that the MHRA, ended up with the same indication (≥18-year-olds; two SD doses to be given 4–12 weeks apart). The SD+SD regimen provided a vaccine efficacy of 60% [20]. It recognized that the conduct of the trials was “sub-optimal with regards to substantial changes to the protocol made after the start of studies, errors in dosing and an unplanned varying dose interval between 4 and 26 weeks” [21]. The EMA acknowledged that there was not enough cases in ≥56-year-olds to provide a vaccine efficacy figure in this age group, but expected protection based on immunogenicity data and on experience with other vaccines [20]. Not surprisingly, this labeling triggered a multitude of different decisions between EU countries as to who should be vaccinated with this vaccine. In a few days, 22 (of 27) EU member states, accounting for 95% of the entire EU population, limited the use of the AstraZeneca vaccine to specific age groups (from up to 55- to up to 70-year-olds) [22]. Although, there were no vaccine efficacy data on ≥56-year-old individuals, health authorities in the various EU countries adapted their decision to local factors (e.g., epidemiology of the pandemic, prioritization schemes, vaccine availability). This became a source of confusion among EU citizens that could hardly understand why depending in the country of residence, individuals would have access or not to the AstraZeneca vaccine that was authorized in the EU with no age restrictions.

To extend the indication to children and adolescents, a phase 2 RCT in 6-17-year-olds started on 2 March.

Publication of exploratory analysis

The results of exploratory analyses of the RCTs pooled data collected up to 7 December were published on 19 February. These showed [23], that vaccine efficacy after a single SD from day 22 to 90 after vaccination was 76%, and that vaccine efficacy was increased when the booster dose was given ≥12 weeks apart (81%) than when administered ≤6 weeks apart (55%). The article, however, did not report on vaccine efficacy in ≥56-years-olds-so no vaccine efficacy in older individuals was available yet. These analyses provided evidence-based support of the approach decided by the UK health authorities in December but could be biased due to the very nature of post hoc analyses [24]. The MHRA updated the product information with the same-pooled data used by the Voysey et al. and, logically, maintained the information that efficacy and safety data were limited in the elderly (≥65-year-olds) [17], even though the lack of vaccine efficacy data also affected to 56-64-year-old individuals.

Vaccine effectiveness comes into play

Between 19 February and 3 March, the picture regarding the usefulness of the AstraZeneca vaccine in the elderly changed dramatically. This was due to the publication of three pre-prints reporting the results of observational studies conducted in the UK [25–27]. The main message was clear: this vaccine was highly effective in the real world to prevent symptomatic disease and hospitalizations. These results led many EU countries to review their decisions on limiting the use of the vaccine to certain age groups. Furthermore, the results of one study [25] was likely used by the Canadian regulatory agency (i.e., Health Canada) to support the use of the vaccine in the elderly, despite acknowledging that vaccine efficacy data on this population group was still lacking [28]. This was followed shortly thereafter by the recommendation to administer the booster dose 12 weeks after the priming dose [29]. Pressure from the epidemiologic situation and the vaccine effectiveness observed in the real-world, seemed to have influenced Canadian regulators to change their minds, since only a few weeks before they were waiting for the results of the large USA phase 3 trial to make a decision [30].
AstraZenea vaccine and SARS-CoV-2 variants

Amid increasing concerns regarding SARS-CoV-2 variants, on 7 February the trial in South Africa reported very poor vaccine efficacy (10%) to prevent mild/moderate COVID-19 due to the B.1.351 variant [31]. The very same day, South Africa stopped the rollout of this vaccine [32], five days before the pre-print of the trial results were published [33]. Despite this, the WHO granted emergency use listing to the vaccine and COVAX rollout [34].

Since the B.1.351 variant has been already spread throughout many African countries, several South African medical leaders [35] raised ethical concerns about the sale of 1 million AstraZeneca vaccine doses to the African Union [36].

On 30 March, an exploratory analysis of cases included in the phase 2/3 RCT run in the UK showed reduced neutralization activity against the SARS-CoV-2 B.1.1.7 variant compared to non-B.1.1.7 variant in vitro; however, the vaccine showed to be clinically efficacious against the B.1.1.7 variant [37]. Due to the wide confidence intervals, no firm conclusions could be drawn on vaccine efficacy against the B.1.1.7 variant [38].

The large phase 3 trial

The large, placebo-controlled RCT conducted in the USA—the one that AstraZeneca pledged to run to form the basis of regulatory submissions—opened new sites in France and in four South American countries. This was to ensure accruing the minimum number of COVID-19 cases that could lead to an estimate of vaccine efficacy in older adults, that the increasing rollout of authorized vaccines in the USA could put in jeopardy. This RCT was the last opportunity to show efficacy in the elderly. Since as of late February 2021, the vast majority of the USA states where the trial was taking place were already vaccinating the elderly, concerns were raised on whether the trial could be successfully completed, as many elderly participants could withdraw from the trial to receive an available COVID-19 vaccine [39].

Fortunately, on 22 March, AstraZeneca reported that this RCT showed an overall vaccine efficacy of 79% at preventing symptomatic COVID-19 and 80% in ≥65-year-old persons [40]. However, scientists and the public were surprised when learning that the US National Institute of Allergy and Infectious Diseases (NIAID) director was informed by the trial’s Data Safety and Monitoring Board that the figures provided by the company were not updated; the Data Safety and Monitoring Board believed that vaccine efficacy should be lower than reported [41]. This was an unprecedented fact: it is difficult to explain that the sponsor did not agree with the Data Safety and Monitoring Board on what results would be made public. On 25 March, AstraZeneca confirmed that the overall vaccine efficacy was 76% and 85% in ≥65-year-old individuals [42]. The published results of this RCT are still awaited, but it will report on vaccine efficacy of two SD given 4 weeks apart—as this was the trial’s dosing interval. This could imply that if this vaccine is authorized for emergency use in the USA or Switzerland, the labeling will likely recommend a 4-week dosing interval— that will help to create confusion since in the rest of the world the vaccine authorized dosing interval is 4 to 12 weeks.

Vaccine combinations

In the middle of a worldwide shortfall of COVID-19 authorized vaccines production, on 8 February a phase 2 trial was initiated to determine the safety and immunogenicity response to several vaccine combinations. Participants were to receive one dose of AstraZeneca or Pfizer/BioNTech vaccine and a second dose of either the same manufacturer or a dose of the other one, given 4 or 12 weeks apart. The results of this trial will be important to support any evidence-based vaccine combinations, something that could be critical in several EU countries as discuss below. However, this study was not designed to solve the problem of many poor-resourced countries, because the Pfizer/BioNTech vaccine is not only expensive but requires storage of undiluted vials at -70°C, rendering this combination not useful for many settings in these countries. The trial was expanded on 19 April to include the Moderna and Novavax COVID-19 vaccines.

Another trial (phase 1/2, NCT04684446) that was registered in late 2020 and that was aimed to assess the combination of one dose of the AstraZeneca vaccine with another of Sputnik V (rAd26-S), has not started yet. It is uncertain whether this small trial could even be initiated.

The identification of unusual thrombosis with thrombocytopenia cases darkens the picture (Supplemental material-4)

The good news provided by the UK observational studies were suddenly replaced by the identification of a serious safety signal: a number of vaccine recipients developed unusual thrombosis with thrombocytopenia in several EU countries. The first two cases were made public in Austria on 7 March 2021 that suspended the use of this vaccine [43]. Four days later, Denmark, Iceland and Norway halted its administration [44]. On 16 March, 24 countries across the world—mainly from the EU but also DR Congo, Indonesia, Thailand and Venezuela—stopped administering the vaccine due to this safety signal [45]. Public trust in the vaccine collapsed in many EU countries [46]. Both the EMA [68] and the WHO [47] stressed that there was not enough evidence to believe in the existence of a causal relationship and that the benefit/risk assessment of the vaccine was clearly positive. This helped many countries to resume AstraZeneca vaccine administration [48] but limiting its use to older adults (≥56-year-old individuals).

On 26 March, the EMA updated the safety information of the vaccine describing the thrombosis with thrombocytopenia cases [49]. Two days after Greinacher et al. [50] published a pre-print with the first 9 cases (4 deaths) that were described as a prothrombotic disorder that clinically resembles heparin-induced thrombocytopenia, but with different serological profile. Three weeks later, the 27 cases notified so far in France were described [51]. The phase 2 RCT in children and adolescents was paused due to this safety signal on 6 April [52].
The 7 April 2021, a critical date for the thrombosis with thrombocytopenia safety assessment

The MHRA and the EMA, the two key regulatory agencies in the AstraZeneca vaccine journey, decided to update the product’s safety information on 7 April 2021, based on the assessment of the available information of cases of thrombotic thrombocytopenia. As of 4 April, there were 222 cases of cerebral venous sinus thrombosis or splanchnic vein thrombosis reported in Europe, after the administration of 35 million AstraZeneca COVID-19 vaccine doses [53]. Both agencies confirmed that, although there was a possible link between the vaccine and this unusual thrombosis with thrombocytopenia cases, the overall benefit/risk ratio remained positive, with no vaccine age restrictions [17,53,54]. The WHO accepted this possible link but highlighted that was not confirmed yet [55].

A timely report showing that the benefits of the vaccine (prevention of ICU admission) far outweigh the harms (unusual thrombosis with thrombocytopenia syndrome) in all age groups and in all three exposure risk scenarios —except in 20–29-year-olds with low exposure risk in which the benefit/risk ratio is more closely balanced [56] —, influenced the UK Joint Committee on Vaccination and Immunization that recommended to offer a different vaccine to 18–29-year-old individuals [57]. This was the first time in which the MHRA and the UK advisory committee were not aligned in their decisions, something common in almost all EU countries, as it has been already mentioned.

As of 8 April, several countries had limited the use of this vaccine to >30- to >65-year-old individuals, whereas Denmark and Norway maintained the suspension of the vaccine [58–61]. Again, with the same information, different countries made different decisions about which age groups should be immunized with this vaccine. It is uncertain whether these countries based their decisions on analyses like the one used by the UK. In any case, two weeks later, the EMA analysis conducted with the available data, showed that the benefit/risk ratio was progressively more favorable as both age and SARS-CoV-2 incidence increase and that the benefits (prevention of hospitalizations, ICU admissions and deaths) only outweigh the risk of thrombosis with thrombocytopenia in the three infection rates scenarios for the elderly [62,63].

Several regulatory agencies updated the AstraZeneca vaccine safety information in mid-April. The EMA added "thrombosis in combination with thrombocytopenia” and "thrombocytopenia” as "very rare” and "common” adverse drug reactions, respectively [64]. Conversely, the MHRA did not mention "thrombosis with thrombocytopenia” in the tabulated list of adverse reactions, although it was pointed out as “very rare” in the text [17]. This was the first time that both agencies were not completely aligned on the type of critical information referred to thus far.

Denmark, which had the pandemic under control and had enough available COVID-19 vaccine doses, decided to suspend the administration of this vaccine on 14 April [65]. Israel followed one week later [66].

Consequences of the thrombotic thrombocytopenia cases

On 9 April, two cases series were published describing what was named as "vaccine-induced thrombotic thrombocytopenia” [67,68]. Eleven days later, Greinacher et al. [69] described in a pre-print how this vaccine could trigger an immune response that ultimately will have prothrombotic consequences.

France decided not to administer the second dose of the AstraZeneca vaccine to those vaccine recipients that were primed with it on 9 April [70]; Germany and Sweden followed some days later [71,72]. These decisions were taken with no evidence from any RCT: the results of the trial combining AstraZeneca and Pfizer/BioNTech vaccines had not yet been reported. The EMA recommended completing the full regimen with an AstraZeneca booster dose [62].

Thrombotic thrombocytopenia cases reported with the Janssen vaccine

The situation became more complex when on 13 April a joint statement of the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) recommended a pause in the administration of the Janssen vaccine while assessing six cases of cerebral venous sinus thrombosis with thrombocytopenia [73]. This prevented the deployment of the Janssen vaccine in the USA, the EU and elsewhere. The first description of a Janssen vaccine-induced thrombotic thrombocytopenia case was published one day later [74].

The EMA assessment of 8 thrombosis with thrombocytopenia cases associated with the administration of the Janssen COVID-19 vaccine, resulted in adding these events as "very rare” adverse reactions in the product information [75]. The FDA assessed 15 cases (3 deaths) and added “thrombosis in large blood vessels combined with thrombocytopenia” as an adverse reaction [75]. Both agencies confirmed the positive benefit/risk ratio of this vaccine [75,76]. This allowed to quickly resuming its deployment in the EU [77], the USA [78] and other countries.

Two other relevant factors

Two of the most striking attractiveness of the AstraZeneca vaccine was the aim of becoming a truly worldwide leader with a not-for-profit price. AstraZeneca was committed to providing 1 billion doses to COVAX through the Serum Institute of India [79]. This objective, however, was rather difficult to achieve, as it was having serious manufacturing issues and exports bans from the Indian government due to the extremely severe second pandemic wave in this country [80,81].

Regarding the vaccine price, although it is something kept confidential, it was known that the 2020 price for the EU and India was €1.78 per dose [82,83]. However, Bangladesh and Uganda paid €3.29 per dose to the Serum Institute of India.
Conclusion

Since April 2020 the AstraZeneca COVID-19 vaccine has experienced a number of significant and unique events that have defined the place this vaccine had in April 2021 in the worldwide fight against SARS-CoV-2 pandemic.

The winding journey of the AstraZeneca vaccine started with a deficient initial clinical development plan in 2020. In fact, it is reasonable to think that this vaccine would have not been authorized in a different pandemic situation (i.e., better epidemiologic indicators) and without a shortage of vaccines, as it lacked efficacy and safety data in the elderly, the population group that needed it most [88]. This latter resulted in different recommendations in many European countries regarding the age groups to be immunized with this vaccine, that created a lot of confusion in many Europeans [22]. The high vaccine effectiveness observed in UK observational studies boosted the confidence of public health officials around the world in this vaccine. However, the occurrence of serious but unusual cases of thrombotic thrombocytopenia—that was the second most critical event—, seriously impacted the trust of many Europeans on this vaccine in mid-March [46], but not so much among UK citizens in the first fortnight of April [89]. The lack of adequate expertise on how to design a robust and clean clinical developed plan within the University of Oxford research team, could have been prevented. However, the link between the vaccine and unusual but severe cases of thrombosis with thrombocytopenia was completely unpredictable.

Although the African Union decided not to buy this vaccine anymore and to replace it with the Janssen vaccine [90] and two developed countries stopped using it, the clear statements from all regulatory agencies and the WHO helped to restore public confidence in this, otherwise, useful vaccine. The AstraZeneca vaccine, the world’s most widely distributed COVID-19 vaccine as of April 2021 [91], has an overall positive benefit/risk ratio when considering the prevented cases of severe COVID-19, death, and likely long COVID-19 syndrome [92], and should play a key role in the fight of this pandemic in many settings.

Funding

This work required no funding

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.therap.2022.07.003.

Disclosure of interest

The author declares that he has no competing interest.

References

[1] Bottaro G. AstraZeneca agrees to produce Oxford University’s coronavirus vaccine candidate on not-for-profit basis. Proactive. 30 April 2020. https://www.proactiveinvestors.co.uk/companies/news/918534/astrazeneca-agrees-to-produce-oxford-universitys-coronavirus-vaccine-candidate-on-not-for-profit-basis-918534.html. [Accessed 25 February 2022].

[2] World Health Organization. COVAX. https://www.who.int/initiatives/acCELERATOR/covax. [Accessed 25 February 2022].

[3] Callaway E. The unequal scramble for coronavirus vaccines. Nature 2020;568:506–7.

[4] AstraZeneca. AstraZeneca advances mass global rollout of COVID-19 vaccine through COVAX. 2 March 2021. https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-advances-mass-global-rollout-of-covid-19-vaccine-through-covax.html. [Accessed 25 February 2022].

[5] Dal-Ré R, Banzi R. When is it reasonable to extrapolate during a pandemic? The case of broad UK delivering for AstraZeneca COVID-19 vaccine. Eur J Intern Med 2021;87:1–2.

[6] Robbins R, Feuerstein A, Branswell H. AstraZeneca Covid-19 vaccine study put on hold due to suspected adverse reaction in participant in the UK. STAT. 8 September 2020. https://www.statnews.com/2020/09/08/astrazeneca-covid-19-vaccine-study-put-on-hold-due-to-suspected-adverse-reaction-in-participant-in-the-u-k/?utm_campaign=stat plus_today&utm_medium=email&hsmi=94835725&hxenc=p2ANqztz-Y9-Y5-2eZ6ZG4fPvYxwXR3oxZLma_smtlDRs82xJxNQzkwKv6GvvcW2iDD90oal00GjJy_jjox35WfQbUsJpIlzGzJAbutm_content=94835725&utm_source=hs_email. [Accessed 25 February 2022].

[7] Grady D, Wu KJ, LaFraniere S. AstraZeneca, under fire for vaccine safety, releases trial blueprints. The New York Times. 19 September 2020. https://www.nytimes.com/2020/09/19/health/astrazeneca-vaccine-safety-blueprints.html. [Accessed 25 February 2022].

[8] AstraZeneca. COVID-19 vaccine AZD1222 clinical trials resumed in the UK. 12 September 2020. https://www.astrazeneca.com/media-centre/press-releases/2020/covid-19-vaccine-azd1222-clinical-trials-resumed-in-the-uk.html. [Accessed 25 February 2022].

[9] Boadlo A. AZ COVID-19 trials resume in Brazil. Reuters. 14 September 2020. https://www.reuters.com/article/us-health-coronavirus-AZ-brazil-idUSKBN26534G [Accessed 25 February 2022].

[10] Rocha E, Dasgupta N, Ravikumar S. Serum Institute gets approval to resume India trial of AZ COVID vaccine. Reuters. 16 September 2020. https://www.reuters.com/article/us-health-coronavirus-serum-institute-idUSKBN2670PP. [Accessed 25 February 2022].
[11] Toyana M. AZ resumes COVID-19 vaccine trials in South Africa, health department says. 15 September 2020. https://www.reuters.com/article/us-health-coronavirus-AZ-safrica-idUSKBN2662WV. [Accessed 25 February 2022].

[12] Steenhuyzen J, O’Darnell C, Chandler V. AZ resumes US COVID-19 vaccine trial and next week J&J prepares to do the same. Reuters. 23 October 2020. https://www.reuters.com/article/us-health-coronavirus-AZ-usa-idUSKBN2782KF. [Accessed 25 February 2022].

[13] Chiaci D. Trump says coronavirus vaccine possible before Nov 3. Reuters. 6 August 2020. https://www.reuters.com/article/us-health-coronavirus-trump-vaccine-usaidUSKCN25221Q. [Accessed 25 February 2022].

[14] AstraZeneca. Biopharma leaders unite to stand with science. Nine CEOs sign historic pledge to continue to make the safety and well-being of vaccinated individuals the top priority in development of the first COVID-19 vaccines. 8 September 2020. https://www.astrazeneca.com/media-centre/press-releases/2020/biopharma-leaders-unite-to-stand-with-science.html. [Accessed 25 February 2022].

[15] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, 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;397:99—111.

[16] Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science 2021;372:[eabg3055].

[17] Gov.UK. 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. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca. [Accessed 25 April 2021].

[18] Gov. UK. Joint Committee on Vaccination and Immunisation: advice on priority groups for COVID-19 vaccination. 30 December 2020. https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/joint-committee-on-vaccination-and-immunisation-advice-on-priority-groups-for-covid-19-vaccination-30-december-2020. [Accessed 25 April 2021].

[19] Laing A. Argentine regulator approves AZ/Oxford COVID-19 vaccine—AZ. Reuters. 30 December 2020. https://www.reuters.com/article/uk-health-coronavirus-argentina-astrazen/argentineregulator-approves-AZ/oxford-covid-19-vaccine-AZ-idUSKBN294273/editi0nredirect-in. [Accessed 25 February 2022].

[20] European Medicines Agency. COVID-19 vaccine AstraZeneca. EMA/57617/2021. EMEA/H/7C/005675. 29 January 2021. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-covid-19-vaccine-astrazeneca_en.pdf. [Accessed 25 February 2022 (5 pp.)].

[21] European Medicines Agency. COVID-19 vaccine AstraZeneca. Assessment report. CHMP. EMA/94907/2021. 29 January 2021. https://www.ema.europa.eu/en/documents/assessment-report/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf. [Accessed 25 February 2022 (181 pp.)].

[22] Dal-Ré R, Lanay O. Public trust on regulatory decisions: the European Medicines Agency and the AZ COVID-19 vaccine label. Vaccine 2021;39:4029—31.

[23] Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet 2021;397:881—91.

[24] Hung IFN, Poland GA. Single-dose Oxford–AstraZeneca COVID-19 vaccine followed by a 12-week booster. Lancet 2021;397:854—5.

[25] Vasililiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021;397:1646—57.

[26] Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford/AstraZeneca vaccines on covid-19 related symptoms, hospitals admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021;373:[n1088].

[27] Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Effectiveness of BNT162b2 and ChAdOx1nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at east 80 years: a test negative, case-control study. Lancet Infect Dis 2021;21:1539—48.

[28] Government of Canada. Health Canada. Regulatory decision summary — AstraZeneca COVID-19 vaccine. 26 February 2021. https://covid-vaccine.canada.ca/info/regulatory-decision-summary-detailTwo.html?linkID=RD500772B&type=rstdlang-en. [Accessed 25 February 2022].

[29] Government of Canada. Archived 5: NACI rapid response: extended dose intervals for COVID-19 vaccines to optimize early vaccine rollout and population protection in Canada. 3 March 2021. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-extended-dose-intervals-covid-19-vaccines-early-rollout-population-protection.html. [Accessed 25 February 2022].

[30] Walsh M, Semenuk I. Getting the jab done: When can Canadians expect to get a COVID-19 vaccine? The Globe and Mail Canada. 22 January 2021. https://www.theglobeandmail.com/canada/article-getting-the-jab-done-when-can-canadians-expect-to-get-a-covid-19/. [Accessed 25 February 2022].

[31] University of Witwatersrand, Johannesburg. Oxford Covid-19 vaccine trial results. 7 February 2021. https://www.wits.ac.za/covid19/covid19-news/latest/oxford-covid-19-vaccine-trial-results.html. [Accessed 25 February 2022].

[32] Herper M. South Africa halts rollout of AstraZeneca’s Covid-19 vaccine after shot falters against variant. STAT 7 February 2021. https://www.statnews.com/2021/02/07/south-africa-halts-rollout-of-astrazenecas-covid-19-vaccine-after-shot-falters-against-variant/. [Accessed 25 February 2022].

[33] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 COVID-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885—98.

[34] World Health Organization. WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out. AstraZeneca/Oxford-developed vaccines to reach countries in the coming weeks. 15 February 2021. https://www.who.int/news/item/15-02-2021-who-lists-two-additional-covid-19-vaccines-for-emergency-use-and-covax-roll-out. [Accessed 25 February 2022].

[35] Venter WDF, Madhi SA, Nel J, Mendelson M, van den Heever A, Moshabela M. South Africa should be using all COVID-19 vaccines available to it urgently. S Afr Med J 2021;111:515—6.

[36] Bhekisisa Team. Why South Africa isn’t using AstraZeneca jabs it bought Health24. 29 March 2021. https://www.news24.com/health24/medical/infectious-diseases/coronavirus/why-south-africa-isnt-using-the-
astraZeneca-jabs-it-bought-20210329. [Accessed 25 February 2022].

[37] Emery KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202102/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. Lancet 2021;397:1351–62.

[38] Sanders R, de Jong MD. Pandemic moves and countermoves: vaccines and viral variants. Lancet 2021;397:1326–7.

[39] Dal-Ré R. Will AstraZeneca be able to provide clinical trial data on its COVID-19 vaccine efficacy in older adults? Br J Clin Pharmacol 2021;87:2405–6.

[40] Kemp A. AZD1222 US phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis. AZ press release. 22 March 2021. https://www.AZ.com/media-centre/press-releases/2021/AZ-us-vaccine-trial-met-primary-endpoint.html [Accessed 25 February 2022].

[41] Joseph A. 'I was sort of stunned': Fauci and U.S. officials say AZ released 'outdated information' from Covid-19 vaccine trial. STAT. 23 March 2021. https://www.statnews.com/2021/03/23/AZ-may-have-used-outdated-information-in-announcing-covid-19-vaccine-results/. [Accessed 25 February 2022].

[42] Kemp A. AZD 1222 US phase III primary analysis confirms safety and efficacy. AZ press release. 25 March 2021. https://www.AZ.com/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html. [Accessed 25 February 2022].

[43] Shields M, Burger L, Heavens L. Austria suspends AZ COVID-19 vaccine batch after death. Reuters. 7 March 2021. https://www.reuters.com/article/article-health-coronavirus-austria-nurse-idUSL8N2L506P. [Accessed 25 February 2022].

[44] COVID: several European countries halt use of AstraZeneca vaccine. DW. 11 March 2021. https://www.dw.com/en/covid-several-european-countries-halt-use-of-astrazeneca-vaccine/a-56835406. [Accessed 25 February 2022].

[45] McCarthy N. Which countries have stopped using AstraZeneca vaccine? Statista 16 March 2021. https://www.statista.com/chart/24420/astrazeneca-vaccine-suspensions/. [Accessed 25 February 2022].

[46] Kelland K. European trust in AstraZeneca COVID-19 vaccine plunges, poll shows. Reuters. 22 March 2021. https://www.reuters.com/article/article-us-health-coronavirus-astrazeneca-confid-idUSKBN2BE009. [Accessed 25 February 2022].

[47] World Health Organization. Statement of the WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee on safety signals related to the AstraZeneca COVID-19 vaccine. 19 March 2021. https://www.who.int/news/item/19-03-2021-statement-of-the-who-global-advisory-committee-on-vaccine-safety-(gacvs)-covid-19-subcommittee-on-safety-signals-related-to-the-astrazeneca-covid-19-vaccine. [Accessed 25 February 2022].

[48] Kupferschmidt K, Vogel G. European countries resume use of AstraZeneca’s COVID-19 vaccine, hoping pause has not dented confidence. Science News. 18 Mar 2021. https://www.sciencemag.org/news/2021/03/european-countries-resume-use-astrazenecas-covid-19-vaccine-hopingpause-has-not-dented. [Accessed 25 February 2022].

[49] European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC). Signal assessment report on embolic and thrombotic events (SMQ) with COVID-19 Vaccine (ChAdOx1-S [recombinant]) – COVID-19 Vaccine AZ (Other viral vaccines). 24 March 2021. EMA/PRAC/157044/2021. https://www.epa.europa.eu/en/documents/prac-recommendation/signal-assessment-report-embolic-thrombotic-events-smq-covid-19-vaccine-chadox1-s-recombinant-covid-en.pdf. [Accessed 25 February 2022 (50 pp.)].

[50] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle P, Eichinger S. A prothrombotic thrombocytopenic disorder resembling heparin-induced thrombocytopenia following coronavirus-19 vaccination. Research Square. 28 March 2021. V1. DOI: 10.21203/rs.3rs.362354/v1. https://www.researchsquare.com/article/rs-362354/v1. [Accessed 25 February 2022].

[51] Gras-Champel V, Liabeuf S, Baud M, Albucher JF, Benkeblia M, Boulay C, et al. French Network of Pharmacovigilance Centres. Atypical thrombosis associated with VaxZerivla® (AstraZeneca) vaccine: data from the French network of regional pharmacovigilance centres. Therapie 2021;76:369–73.

[52] Nair A, Mishra M, Arkikap P, Reese C, Ramakrishnan M. Oxford pauses COVID-19 vaccine study in kids, awaits more data on blood clot issues. Reuters. 6 April 2021. https://www.reuters.com/article/uk-health-coronavirus-britain-vaccine-idUSKBN2BT2F5. [Accessed 25 February 2022].

[53] AstraZeneca’s COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 7 April 2021. https://www.ema.europa.eu/en/documents/prac-assess-committee-on-vaccine-safety-european-biologicals-refers-astra-zeneca-covid-19-vaccine-emergency-use-safety-and-efficacy-information-in-announcing-covid-19-vaccine-results. [Accessed 25 February 2022].

[54] Gov UK. MHRA issues new advice, concluding a possible link between COVID-19 Vaccine AZ and extremely rare, unlikely to occur blood clots. Press release. 7 April 2021. 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. [Accessed 25 February 2022].

[55] World Health Organization. Interim statement of the COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety on AstraZeneca COVID-19 vaccine. 7 April 2021. https://www.who.int/news/item/07-04-2021-interim-statement-of-the-covid-19-subcommittee-of-the-who-global-advisory-committee-on-vaccine-safety. [Accessed 25 February 2022].

[56] University of Cambridge. Winton Centre for Risk and Evidence Communication. Communicating the potential benefits and harms of the AstraZeneca COVID-19 vaccine. 7 April 2021. https://wintoncentre.maths.cam.ac.uk/news/communicating-potential-benefits-and-harms-astra-zeneca-covid-19-vaccine/?utm_source=Nature+Briefing&utm_campaign=e241758a-brief-fing-dy-20210409&utm_medium=email&utm_term=0_c9ffdd3973-e0241758a-43511561. [Accessed 25 February 2022].

[57] Gov.UK. Joint Committee on Vaccination and Immunization. JCVI statement on use of the AstraZeneca COVID-19 vaccine. 7 April 2021. https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcv1-statement/jcv1-statement-on-use-of-the-astrazeneca-covid-19-vaccine-7-april-2021. [Accessed 25 February 2022].

[58] Davis N, Henley J. What do I need to know about the Oxford/AZ vaccine? The Guardian. 7 April 2021. https://www.theguardian.com/world/2021/apr/07/what-do-i-need-to-know-about-the-oxfordastrazeneca-vaccine. [Accessed 25 February 2022].

[59] Henley J. Spain, Belgium and Italy restrict AstraZeneca Covid vaccines to older people. The Guardian. 8 April 2021. https://www.theguardian.com/society/2021/apr/08/spain-belgium-and-italy-restrict-astrazeneca-covid-vaccine-to-older-people. [Accessed 25 February 2022].

[60] South Korea Suspends Use Of AstraZeneca’s COVID-19 Vaccine, Vaccination Program Disrupted. VOI. 8 April 2021. https://voi.id/en/news/43024/south-korea-suspends-use-of-
astazenecas-covid-19-vaccine-vaccination-program
-disrupted. [Accessed 25 February 2022].
[61] Morales J, Davies E. Philippines suspends use of AstraZeneca people under 60. Reuters. 8 April 2021. https://www.usnews.com/news/world/articles/2021-04-08/philippines-suspends-use-of-astrazeneca-vaccine-for-people-under-60. [Accessed 25 February 2022].
[62] European Medicines Agency. Assessment report. Procedure under article 5(3) of Regulation(EC) No 726/2004. Chimpanzee adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-2). 23 April 2021. EMA/CHMP/214855/2021. https://www.ema.europa.eu/en/documents/referral/use-vaxzevria-prevent-covid-19-article-53-procedure-assessment-report_en.pdf. [Accessed 25 February 2022 (21 pp.)].
[63] European Medicines Agency. Annex to Vaxzevria Art 5.3—visual risk contextualization. 23 April 2021. EMA/234525/2021. https://www.emea.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf. [Accessed 25 February 2022 (12 pp.)].
[64] European Medicines Agency. Vaxzevria (previously COVID-19 vaccine AstraZeneca). EPAR—Medicine overview. Summary of Products characteristics. 16 April 2021. https://www.ema.europa.eu/en/documents/product-information/vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-product-information_en.pdf. [Accessed 25 February 2022 (37 pp.)].
[65] Danish Health Authority. Denmark continues its vaccine rollout without the COVID-19 vaccine from AstraZeneca. 14 April 2021. https://www.sst.dk/en/english/news/2021/denmark-continues-its-vaccine-rollout-without-the-covid-19-vaccine-from-astrazeneca. [Accessed 25 February 2022].
[66] Heller J, Rabinovitch A. With enough supplies, Israel looks to re-route AstraZeneca vaccine delivery. SWI. 21 April 2021. https://www.swissinfo.ch/eng/reuters/with-enough-supplies-israel-looks-to-re-route-astrazeneca-vaccine-delivery/46552996. [Accessed 25 February 2022].
[67] Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrie PA, Eichinger S. Thrombotic-Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. N Engl J Med 2021;384:2092–101.
[68] Schultz NH, Sorvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021;384:2124–30.
[69] Greinacher A, Seleng K, Wescbe J, Handtke S, Palankar R, Aurich K, et al. Towards understanding ChAdOx1 nCoV-19 vaccine-induced immune thrombotic thrombocytopenia (VITT). Research Square. 20 April 2021. V1. DOI: 10.21203/rs.3.rs.440461/v1. https://www.researchsquare.com/article/rs-440461/v1. [Accessed 25 February 2022].
[70] AstraZeneca: France says under 55s to receive different second dose of the COVID-19 vaccine. 9 April 2021. https://www.euronews.com/2021/04/09/astrazeneca-france-says-under-55s-to-receive-different-second-dose-of-the-covid-19-vaccine. [Accessed 25 February 2022].
[71] Germany to give different second vaccine to AstraZeneca recipients under 60. France 24. 14 April 2021. https://www.france24.com/en/europe/20210414-germany-to-give-different-second-vaccine-to-astrazeneca-recipients-under-60. [Accessed 25 February 2022].
[72] Swedes under 65 to be given alternative to AZ vaccine for second dose. Reuters. 20 April 2021. https://www.reuters.com/world/europe/swedes-under-65-be GIVEN-ALTERNATIVE-AZ-VACCINE-SECOND-DOSE-2021-04-20/. [Accessed 25 February 2022].
[73] Marks P. Joint CDC and FDA statement on Johnson & Johnson COVID-19 vaccine. https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine. [Accessed 25 February 2022].
[74] Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic thrombocytopenia after Ad26.COV2.S vaccination. N Engl J Med 2021;384:1964–5.
[75] COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets. 20 April 2021. https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood. [Accessed 25 February 2022].
[76] Food and Drug Administration. Fact sheet for healthcare providers administering vaccine. Emergency Use authorization (EUA) of the Janssen COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 23 April 2021. https://www.fda.gov/media/146304/download. [Accessed 25 February 2022].
[77] Johnson & Johnson COVID-19 vaccine roll-out to resume in Europe following European Medicines Agency (EMA) review. 20 April 2021. https://www.janssen.com/euma/sites/www.janssen.com.euma/files/johnson_johnson_covid_19_vaccine_roll_out_to_resume_in_europe_following_european_medicines_agency_ema_review.pdf. [Accessed 25 February 2022 (4 pp.)].
[78] Centers for Disease Control and Prevention. FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review. 23 April 2021. https://www.cdc.gov/media/releases/2021/fda-cdc-lift-vaccine-use.html. [Accessed 25 February 2022].
[79] Padma TV. India’s COVID-vaccine woes —by the numbers. Nature News. 15 April 2021. https://www.nature.com/articles/d41586-021-00996-y&utm_source=Nature-Briefing&utm_campaign=384b97fde-briefing-dy-20210416&utm_medium=email&utm_term=0_c9df3d3973-384b97fde-43511561. [Accessed 25 February 2022].
[80] AstraZeneca to reduce EU Covid vaccine deliveries following production problems. France 24. 14 March 2021. https://www.france24.com/en/europe/20210314-covid-19-astrazeneca-to-reduce-eu-vaccine-deliveries-following-production-problems. [Accessed 25 February 2022].
[81] Safi M, Kirk A. Revealed: big shortfall in Covax Covid vaccine-sharing scheme. The Guardian 22 April 2021. https://www.theguardian.com/world/2021/apr/22/revealed-big-shortfall-in-covax-covid-vaccine-sharing-scheme. [Accessed 25 February 2022].
[82] Boselie S. Belgian minister tweets EU’s COVID vaccine price list to anger of manufacturers. The Guardian 18 December 2020. https://www.theguardian.com/world/2020/dec/18/belgian-minister-accidentally-tweets-eus-covid-vaccine-price-list. [Accessed 25 February 2022].
[83] India agrees ‘significantly lower’ AstraZeneca vaccine price. Reuters 11 March 2021. https://www.reuters.com/article/health-coronavirus-india-idUSKBN2831H1. [Accessed 25 February 2022].
[84] Paun C, Furlong A. Poorer countries hit with higher price tag for Oxford/AstraZeneca vaccine. Politico. 22 February 2021. https://www.politico.eu/article/astrazeneca-vaccine-cost-higher-in-poorer-countries-coronavirus/. [Accessed 25 February 2022].
[85] Le Roux K. South Africa gets 1.5m AstraZeneca Covid-19 vaccine doses from India. CapeTalk. 7 January 2021. http://www.capetalk.co.za/articles/405562/breaking-news-sa-gets-1-5m-astrazeneca-covid-19-vaccine-doses-from-india. [Accessed 25 February 2022].
[86] Beaumont P. Oxford AstraZeneca vaccine to be sold to developing countries at cost price. The Guardian. 23 November 2020. https://www.theguardian.com/global-development/2020/
nov/23/oxford-astrazeneca-results-covid-vaccine-developing-countries. [Accessed 25 February 2022].

[87] Mancini DP. AstraZeneca vaccine document shows limit of no-profit pledge. Financial Times. 7 October 2020. https://www.ft.com/content/c474f9e1-8807-4e57-9c79-6f4af145b686. [Accessed 25 February 2022].

[88] Topol E. Paul Offit’s Biggest Concern About COVID Vaccines. Medscape. 9 September 2020. https://www.medscape.com/viewarticle/936937. [Accessed 25 February 2022].

[89] Kings College London. Preference for AZ vaccine declines—but vaccine confidence undented. News Centre. 28 April 2021. https://www.kcl.ac.uk/news/preference-for-az-vaccine-declines-but-vaccine-confidence-undented. [Accessed 25 February 2022].

[90] African Union drops plans to secure vaccines from India. BBC 8 April 2021. https://www.bbc.com/news/live/uk-56672556. [Accessed 25 February 2022].

[91] Holder J. Tracking coronavirus vaccinations around the world. 22 April 2021. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html. [Accessed 25 February 2022].

[92] Gov.UK. UK Health Security Agency. The effectiveness of vaccination against long COVID: A rapid evidence briefing. 15 February 2022. https://www.gov.uk/government/news/ukhsa-review-shows-vaccinated-less-likely-to-have-long-covid-than-unvaccinated. [Accessed 25 February 2022].