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Heterologous COVID-19 Vaccination in Spain: A Case Study of Individual Autonomy in the Real World

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A B S T R A C T

In Spain, 1.5 million essential < 60-year-old workers were vaccinated with a first AstraZeneca vaccine dose. After assessing the cases of thrombosis with thrombocytopenia associated to this vaccine, the European Medicines Agency (EMA) supported the administration of 2 doses of the AstraZeneca vaccine with no age restrictions. Nevertheless, Spain decided not to administer the second dose of this vaccine to < 60-year-olds. The government sponsored a clinical trial (CombiVacS) to assess the immunogenicity response to a Pfizer/BioNTech vaccine dose in adults primed with the AstraZeneca vaccine. The positive results backed the Public Health Commission and the Spanish Ministry of Health to offer the Pfizer/BioNTech vaccine as the booster. Nevertheless, regional public health authorities—responsible for administering vaccines—believed that, following the EMA’s decision, an AstraZeneca booster dose should be given. The public confrontation of these 2 positions forced the Spanish Health Ministry to request the signature of an informed consent form to those individuals willing to receive the AstraZeneca vaccine booster and rejecting the Pfizer/BioNTech vaccine dose. Eventually, it was decided that these essential workers could choose the vaccine but signing an informed consent form. All relevant information was posted on the Ministry of Health and regional health authorities’ websites and provided to potential vaccine recipients at vaccination sites. Most individuals (> 75%) chose the AstraZeneca vaccine: perhaps because they likely trusted the EMA more than the CombiVacS results. This unprecedented and massive exercise of individual autonomy about the choice of COVID-19 vaccines from 2 different platforms has shown that adequately informed persons can autonomously weigh their options, regardless of government decisions. Exercising individual autonomy may contribute to the success of future COVID-19 booster vaccination campaigns.

Keywords: adults, AstraZeneca, autonomy, COVID-19, heterologous vaccination, mix-and-match, Pfizer/BioNTech, thrombosis with thrombocytopenia, vaccines.

VALUE HEALTH. 2022; 25(5):770–772

Introduction

Among the several million individuals who were vaccinated for COVID-19 with the AstraZeneca vaccine in Spain, 1.5 million essential < 60-year-old workers (eg, teachers, firemen, police officers) were vaccinated with a first dose. Throughout March 2021, several concurrent episodes of thrombosis with thrombocytopenia were described in Europe. After a thorough assessment of these cases, the European Medicines Agency (EMA) supported the administration of 2 doses of this vaccine with no age restrictions (April 7-23, 2021). Nevertheless, Spain and other countries decided to administer the second dose only to older adults. Based on the EMA decision, on April 30, 2021, 17 Spanish scientific societies supported the administration of a booster AstraZeneca vaccine dose to those recipients of the first one.

The Spanish Government Role

The labels of all COVID-19 vaccines available in the European Union acknowledged that there were no data on the interchangeability of these vaccines. Although several countries such as France and Germany were offering a messenger RNA vaccine second dose to adults up to a certain age limit that were primed with an AstraZeneca vaccine dose, the Spanish Ministry of Health funded (via the Instituto de Salud Carlos III) the “CombiVacS” trial to base its decision on scientific data. On April 24 to 30, 2021, < 60-year-old adults primed with the AstraZeneca vaccine were randomized (2:1 ratio) to receive a Pfizer/BioNTech vaccine dose (n = 448) or observation, that is, no booster vaccine dose (n = 225). The primary endpoint was the anti-SARS-CoV-2 spike protein antibody response measured by immunoprecipitation, at day 14. Reactogenicity was assessed up to day 7 after vaccination. CombiVacS was aimed to assess whether the heterologous administration of the Pfizer/BioNTech vaccine booster dose could elicit strong immunogenicity response with an acceptable reactogenicity profile. Nevertheless, the trial design precluded direct comparison with a concurrent control group with a vaccination schedule that mimics the real world, a 2-dose regimen. On May 18, 2021, the results of this trial were presented in a 1-hour press conference in which investigators explained in detail the results attained, its consequences in
public health decision making, and its limitations. This news was widely covered by the lay and scientific media throughout the country and abroad.

**Regional Governments Response**

The good immunogenicity and acceptable reactogenicity results of the trial backed Spain’s Public Health Commission and the Spanish Health Ministry decision to offer the Pfizer/BioNTech vaccine as a booster dose. However, health authorities of several Spanish regions—ultimately responsible of vaccine administration in their territories—claimed that, following the EMA’s decision, an AstraZeneca vaccine booster dose should be given. The public confrontation of these 2 positions forced the Spanish Health Ministry to request—endorsed by the Spanish Bioethics Committee—for the first time in the vaccination campaign to sign an informed consent form for those individuals willing to receive a second dose of the AstraZeneca vaccine and rejecting the Pfizer/BioNTech dose. Nevertheless, some regional health authorities decided to allow these individuals to choose which vaccine they wanted to receive, but after signing an informed consent form regardless of the vaccine chosen. The information posted on the regional health authorities websites and provided to potential vaccine recipients at vaccination sites referred, among other things, to the infrequent risk of thrombosis with thrombocytopenia associated to the AstraZeneca vaccine. To convince the highest number of essential workers that the Pfizer/BioNTech booster dose was the best approach, the Ministry of Health further reported that there had been 20 cases of thrombosis with thrombocytopenia (with 4 deaths) among the 5 million individuals vaccinated with 1 dose of this vaccine in Spain. Nevertheless, the Ministry of Health failed to report the number of cases of thrombosis with thrombocytopenia after the administration of the second dose of the AstraZeneca vaccine observed in other countries such as the United Kingdom. The conduct of CombiVacS had a secondary consequence that was not anticipated by most interested individuals. This trial forced to delay the administration of the booster dose from 12 weeks to 16 weeks for the 1.5 million essential < 60-year-old workers. This meant that all these individuals received either AstraZeneca or Pfizer/BioNTech booster doses on an off-label fashion. It should be highlighted, however, that Canada has been administering 2 doses of these vaccines with a 16-week interval since March 2021, although no data have been reported supporting the 16-week gap between the 2 vaccine doses. Even though this delay will most likely have no negative consequences for individual or public health, many essential workers were surprised that they had to wait 16 weeks for the second vaccine dose after receiving their first inoculation. Overall, the vaccination campaign among essential workers has been a success.

**The Essential < 60-Year-Old Workers Made Their Decision**

Most essential < 60-year-old workers (≈ 75%) chose to receive a booster dose of the AstraZeneca vaccine, perhaps because they likely trusted the EMA more than CombiVacS results. Since late 2020, clinical experts echoed by the media in Spain have reported on the EMA’s procedures and decisions—adding to the respect and credibility of the EMA. In addition, these < 60-year-old individuals were highly motivated and had access to enough information to make up their minds, although many were negatively surprised to have to sign an informed consent document. The information on this topic was extensively disseminated through media and social media and for some days was one of the most important and discussed news.

Now that the European Union will not acquire more AstraZeneca COVID-19 vaccine doses, it is obvious that if a booster dose is needed in the future, all those that have completed the 2-dose regimen with this vaccine will have to be boosted with a heterologous vaccine. Nevertheless, future public health decisions on the use of heterologous prime-boost COVID-19 vaccination will be based on comparative data from other trials.

**Conclusions**

This unprecedented and massive exercise of individual autonomy regarding the choice of COVID-19 vaccines from 2 different platforms (viral vector [AstraZeneca] and messenger RNA [Pfizer/BioNTech]) has shown that adequately informed persons can autonomously weigh their options, regardless of country government recommendations. Furthermore, public health authorities should consider that, when feasible, allowing people to make their choices can further contribute to the success of future booster vaccination campaigns, something that was already shown in a 2-dose vaccination empirical exercise. Individual preferences for COVID-19 vaccine choice are of special interest because several high-income countries are rolling out (eg, Israel) or thinking to offer (eg, France, Germany, United States) a third booster COVID-19 vaccine dose.

**Article and Author Information**

**Accepted for Publication:** December 6, 2021
**Published Online:** February 5, 2022
**doi:** https://doi.org/10.1016/j.jval.2021.12.011

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**Conflict of Interest Disclosures:** Dr Farré reported participation on a Data and Safety Monitoring Board or Advisory Board of the CombiVacS trial (unpaid). No other disclosures were reported.

**Funding/Support:** The authors received no financial support for this research.
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