



## **The Importance of Health Communication during Emergencies: The Mix-and-Match Question**

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The Mix-and-Match approach, adopted by several European and non-European countries during the current COVID-19 vaccination rollout, consists of mixing different brands of COVID-19 vaccines to complete one's vaccination schedule.<sup>1</sup> Dose mixing occurs independently of the mechanism of action of COVID-19 vaccines.<sup>1</sup> Particularly, mixing processes can include vaccines using the same technology, such as Pfizer and Moderna, or using different technologies, i.e. AstraZeneca and Pfizer.<sup>1</sup>

Such an approach has been introduced as early as January 2021 in the United Kingdom's vaccination guidelines.<sup>2</sup> Up to date, several countries have adopted the mix-and-match method, namely, Canada, Denmark, France, Germany, Italy, Bahrain, Finland, Norway, South Korea, Spain, Sweden, United Arab Emirates (UAE), and the United States (US).<sup>3,4</sup> Nonetheless, the approaches taken by the previously mentioned countries in mixing vaccines vary extensively.

### Bahrain:

On June 4, 2021, the government announced that eligible individuals could receive booster vaccines from Pfizer, Moderna or Sinopharm independently of the first vaccination dose.<sup>3</sup>

### Canada:

On June 1, 2021, the Canadian Public Health Agency has advised on COVID-19 vaccine's interchangeability.<sup>5</sup> According to the recommendations of the National Advisory Committee on Immunization (NACI), individuals who receive the first dose of the AstraZeneca vaccine can receive either mRNA or AstraZeneca vaccine as a second dose, unless there are contraindications.<sup>5</sup> Additionally, individuals receiving the first dose of an mRNA vaccine should receive the same vaccine upon the second dose, unless not readily available or knowledge about the first dose of the mRNA vaccine injected is lacking.<sup>5</sup> Such decisions have been taken by NACI based on the available knowledge regarding the adverse effects resulting from dose-mixing and the AstraZeneca vaccine and the immune responses resulting from mixing the AstraZeneca vaccine with the Pfizer one. The NACI has made such decisions based on the available knowledge on the adverse reactions resulting from dose-mixing, immune responses following the mixture of AstraZeneca and Pfizer vaccines, and side-effects arising from the AstraZeneca vaccine.<sup>5</sup>

### Denmark:

On March 11, 2021, the Danish Health Agency suspended the use of the AstraZeneca vaccine.<sup>6</sup> On April 14, 2021, the same mentioned that the vaccination rollout would continue without the AstraZeneca vaccine and *"Those who have received the first injection with AstraZeneca will later receive an invitation to vaccination with another vaccine"*.<sup>6</sup> Such measures emerge from the position taken by the European Medicines Agency (EMA) regarding the AstraZeneca vaccine and the national pandemic situation.<sup>6</sup>

### Finland:

On April 14, 2021, the Finnish Institute of Health and Welfare (THL) extended the decision concerning the suspension of the AstraZeneca vaccine below the age of 65.<sup>7</sup> The THL considered the possibility of using an mRNA vaccine following the first dose of AstraZeneca vaccine for those aged below 65.<sup>7</sup> On May 27th 2021, the THL declared that individuals above the age of 65 could take an mRNA vaccine as their second dose following a first dose of AstraZeneca vaccine in exceptional circumstances.<sup>8</sup> On the same date, the THL recommended that *"Those under the age of 65 will be given only the mRNA vaccines – the Moderna and Biotech-Pfizer vaccines. The mRNA vaccines are administered also to those under 65 who were given the AstraZeneca vaccine as their first dose."*<sup>8</sup> Such decisions have been based on the

available research, epidemiological situation, and the risk of blood coagulation for younger individuals.<sup>8</sup>

#### France:

On April 5, 2021, the French National Authority for Health (Haute Autorité De Santé - HAS) has recommended that individuals under the age of 55 who have received the first dose of the AstraZeneca vaccine shall be injected with an mRNA vaccine upon the second one with a 12-week interval.<sup>9</sup> Such a decision has been taken considering several elements, namely:

- The HAS recommendation of March 19th 2021 concerning the use of the AstraZeneca vaccine for individuals of and above the age of 55;<sup>9</sup>
- The PRAC conclusions of the 7th of April 2021 concerning the AstraZeneca vaccine and side effects;<sup>9</sup>
- The impossibility of excluding a class effect;<sup>9</sup>
- The lack of knowledge regarding the protective nature of a single dose of the AstraZeneca vaccine;<sup>9</sup> and
- Animal studies and the scientific rationale behind the mix-and-match approach combining an mRNA vaccine with an adenoviral one.<sup>9</sup>

#### Germany:

On April 13, 2021, Federal and Regional health Ministers agreed that individuals below the age of 60 who have received upon first dose the AstraZeneca vaccine would be injected upon second dose an mRNA vaccine.<sup>10,11</sup>

#### Italy:

On June 13, 2021, the Italian Medicines Agency's (Agenzia Italiana del Farmaco - AIFA) Technical Scientific Commission (CTS) approved the mix-and-match method for individuals under the age of 60 vaccinated who received as first dose the AstraZeneca vaccine.<sup>12</sup> Accordingly, an mRNA vaccine shall be injected from 8 to 12 weeks after receiving the AstraZeneca vaccine.<sup>12</sup> Such a decision has been issued on the basis of:

- Scientific studies suggesting a good reactogenicity and an enhanced antibody response;<sup>12</sup>
- The Italian epidemiological scenario;<sup>12</sup>
- An analysis of the Summary of Product Characteristics (SmPC);<sup>12</sup> and
- The need to ensure a smooth vaccine rollout.<sup>12</sup>

#### South Korea:

On June 18, 2021, South Korea announced that due to delays in shipments, individuals who received the first dose of the AstraZeneca vaccine will receive the Pfizer one as second dose.<sup>4</sup>

#### Spain:

On May 18, 2021, the Spanish Comisión de Salud Pública (Public Health Commission) agreed that individuals under the age of 60 who received the first dose of the AstraZeneca vaccine receive a second dose of the Pfizer vaccine (12 weeks interval).<sup>13</sup> Following the Consejo Interterritorial del Sistema Nacional de Salud (CISNS) of May 19, 2021, it was given the possibility for individuals to choose whether to receive a second dose of Pfizer or AstraZeneca vaccine.<sup>13</sup> In the latter scenario, individuals must sign a consent form which highlights their knowledge regarding side-effects.<sup>13</sup> Such a measure has been taken to avoid individuals from remaining unvaccinated.<sup>13</sup>

#### Sweden:

On April 20, 2021, the Swedish health agency declared that individuals under the age of 65 who received the first dose of the AstraZeneca vaccine shall be injected a different one upon second dose.<sup>3</sup>

#### Norway:

After the suspension of the AstraZeneca vaccine on March 10, 2021, the Ministry of Health announced on April 23, 2021, that individuals who received the AstraZeneca vaccine would be offered an mRNA vaccine upon the second dose (interval: 12 weeks).<sup>14,15</sup>

Given the objective of vaccinating many people rapidly, mixing mRNA vaccines is possible.<sup>15</sup>

#### United Arab Emirates:

UAE has allowed individuals vaccinated with the Sinopharm vaccine to receive a booster COVID-19 Pfizer shot.<sup>3</sup>

#### United Kingdom:

During January 2021, the UK established that individuals could receive different vaccine doses in exceptional circumstances such as the unavailability of the vaccine or a lack of knowledge about the vaccine injected upon the first dose.<sup>3,16</sup>

On June 28, 2021, the UK health secretary presented the results of the Oxford Com-COV study on dose-mixing, mentioning that the mix-and-match approach might lead to better immune responses and flexibility during the vaccination rollout.<sup>17</sup> Specifically, a randomized controlled trial with 830 individuals from the age of 50 were delivered either two doses of AstraZeneca vaccine, two doses of Pfizer vaccine, or one dose of each, 28 or 84 days apart. The trial found that [all schedules resulted in SARS-CoV-2 anti spike IgC concentrations that were at least as high as those of the currently followed schedule of Pfizer doses](#), which has been effective at preventing symptomatic COVID-19.<sup>18</sup> Of the schedules, two doses of [Pfizer were found to build the most immunogenicity](#), while two [AstraZeneca doses were the least immunogenic](#).<sup>18</sup> A dose of AstraZeneca followed by a dose of Pfizer resulted in [the largest increase in vaccine-antigen response T-cells](#).<sup>18</sup>

#### United States:

To date, the CDC has claimed that COVID-19 vaccines are not interchangeable. Nonetheless, during January 2021, the same updated its guidance specifying that mRNA vaccines can be mixed in exceptional circumstances such as the unavailability of the vaccine and the lack of knowledge about the mRNA vaccine injected upon first dose (interval: minimum 28 days).<sup>19,20</sup> Furthermore, the CDC mentions that *“In situations where the same mRNA vaccine product is temporarily unavailable, it is preferable to delay the second dose (up to 6 weeks) to receive the same product than to receive a mixed series using a different product.”*<sup>20</sup>

A summary of the previously described national approaches can be found in the appendix.

As can be seen, there is no global - or European - consensus on best practice. Indeed, the previously mentioned decisions have provoked opposite reactions among the scientific community and the public, with some supporting the mix-and-match approach based on immunological and logistical benefits and others claiming the lack of extensive scientific evidence.<sup>1</sup> The absence of European and non-European guidance regarding the employment of different vaccines and the lack of a common evidence-based approach contribute to the public's concerns, conceivably increasing hesitancy levels and decreasing vaccine uptake among the population. The lack of clear communication has the potential to increase mistrust and decrease public confidence in the governmental responses - and vaccines themselves. As recognised by the CISNS, utilising the mix-and-match approach without giving individuals the opportunity to choose might also lead to the refusal of the second vaccination dose.<sup>13</sup>

ASPHER, as Europe's representative organisation for Schools of Public Health, recognises the need for well-designed health communication strategies during health emergencies and, in particular, vaccination rollout. In this regard, health communication is crucial in influencing the health and wellbeing of communities.<sup>21</sup> Furthermore, as established by the SAGE Working Group on Vaccine Hesitancy, the communication environment is a pivotal contextual influence of vaccine hesitancy.<sup>22</sup> Moreover, ASPHER is deeply concerned by the lack of consistent and strong evidence when informing decision-making. The Com-COV study clearly suggests no detriment to immune responses through the mixing of vaccines; however, the design and conduct of the clinical trial falls short of providing adequate rationale for the benefits, risks and safety of mixing doses. Further follow up is needed if the claim that mixing vaccines strengthens immune response. It is possible that the heightened response to an mRNA dose following a non-mRNA vaccine may not be much greater than a single mRNA injection. The study is not sufficiently statistically powered to demonstrate safety of the mixed regimes. A similar problem was levelled at a recent Spanish study, the CombiVacS study, a phase 2, multicentre, randomised, controlled trial done at five university hospitals in Spain. The design of this study also lacks the statistical power and follow-up framework to detect any low-frequency adverse effects, nor can it demonstrate greater relative immunogenicity arising from heterologous vaccination schedules (Pfizer administered as second dose in participants with a first dose of AstraZeneca).

Firstly, ASPHER advocates for the execution and widespread availability of empirical studies.<sup>23</sup> Longer term studies with adequate statistical power are needed to demonstrate the combined immunological response and to determine whether it is lasting. We need to establish more widespread and rapid empirical studies. Stronger evidence should guide coherent global action and inform decision-making. The current real world data could inform global guidance regarding dose mixing.

Moreover, ASPHER calls for the collaboration and coordination of credible sources such as public health organisations and authorities, physicians and scientists, the government, the media environment, and the public when conducting such empirical studies and presenting the results.<sup>24,25</sup> ASPHER highlights the need of recognising the public as a legitimate partner in decision-making.<sup>24</sup> The latter can be ensured by showing respect for the public's concerns and demonstrating that decisions keep into account their worries.<sup>24</sup>

**Secondly, ASPHER further recognises the influence of traditional and modern media environments on the current infodemic and vaccine uptake.<sup>22</sup> Given the former, it is essential to cooperate with such platforms by establishing long-term trusting relationships and providing appropriate information for each media platform based on the different audiences.<sup>24</sup> Repeating key positive messages, providing up-to-date information, and addressing false information is also crucial.<sup>24</sup>**

**Thirdly, ASPHER calls for clear messages.<sup>24</sup> Communication strategies shall avoid inaccuracies, mixed and conflicting information, and late communication.<sup>24</sup>**

**Vaccine regulatory agencies and National Immunisation Advisory Committees should be mindful of the benefits of international consensus.**

**European and global public health authorities shall be on the front-line and guide national action rather than waiting for it.**

**Ultimately, ASPHER recognises the need to effectively train a broad range of public health professionals in the health communication field. ASPHER acknowledges the role of Schools of Public Health in teaching and distributing health communications and draws attention to the ASPHER COVID-19 Task Force's works on vaccine hesitancy, vaccinology, and competencies.**

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## Appendix

**Table 1:** Mix-and-match method and country positions/approaches - summary.

Country	First Dose	Second Dose	Age-groups
Bahrain	Any COVID-19 vaccine	Pfizer / Moderna / Sinopharm ( <i>booster shot</i> )	
Canada	AstraZeneca  mRNA vaccine (Pfizer/Moderna)	mRNA vaccine  Different mRNA vaccine ( <i>If vaccine upon first dose unknown or not available</i> )	
Denmark	AstraZeneca	Different vaccine (not specified)	
Finland	AstraZeneca	mRNA vaccine	< 65 years old
France	AstraZeneca	mRNA vaccine	< 55 years old
Germany	AstraZeneca	mRNA vaccine	< 60 years old
Italy	AstraZeneca	mRNA vaccine	< 60 years old
South Korea	AstraZeneca	Pfizer ( <i>Shipment delays</i> )	
Spain	AstraZeneca	Pfizer / AstraZeneca ( <i>individual to choose</i> )	<60 years old
Sweden	AstraZeneca	Different vaccine (not specified)	< 65 years old
Norway	AstraZeneca	mRNA vaccine	
United Arab Emirates (UAE)	Sinopharm	Pfizer ( <i>booster shot</i> )	
United Kingdom (UK)	Not specified	Not specified	See reference 17
United States (US)	mRNA vaccine	Different mRNA vaccine ( <i>If vaccine upon first dose unknown or not available</i> )	