Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Why promoting a COVID-19 vaccine booster dose?

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French COVID-19 vaccination campaign started on the 27th of December 2020, first with long-term care facility residents and health care workers, then progressively extended by age and risk factors for severe COVID-19 to all adults on the 31st of May 2021 and to 12-17-year-olds on the 15th of June 2021. As of the 17th of September 2021, more than 50 million French people (75% of the total population) have received at least one dose of the four European Medicine Agency approved COVID-19 vaccines: mRNA BNT162b2 (Comirnaty®, Pfizer-BioNTech), mRNA-1273 (Spikevax®, Moderna), ChAdOx1 nCoV-19 (Vaxzevria®, AstraZeneca-Oxford University), and Ad26.COV2-S (COVID-19 Vaccine Janssen®, Janssen-Cilag).

French Health authorities approved a booster dose of mRNA vaccine (independently of the vaccine received in the primary scheme) for those over 65 and those at high risk of developing severe forms of COVID-19. This booster campaign has started to roll out on the 1st of September 2021. More recently, on the 6th of October 2021, the recommendation was extended to healthcare professionals and relatives of immunocompromised patients.

A distinction needs to be made between "booster" and "additional" doses. "Booster" doses are for people who responded adequately to primary vaccination in order to restore protection after it would have waned. "Additional" doses concern immunocompromised people who did not respond adequately to the standard primary vaccination. These additional doses have been administered to severely immunocompromised people since the 11th of April in France.

Expected objectives of a booster dose

The choice for a booster campaign mostly relies on the association of the spread of Delta variant of concern (VOC) and first available data on the waning of humoral immunity following vaccination.

Several studies have shown that COVID-19 vaccination is able to induce a robust immune response towards the spike protein of SARS-CoV-2 with the generation of T and B cell-antibody responses. However, the duration of this immune response is still unknown and it is not clear whether a waning of neutralising antibody levels would occur as it has been reported around six months post-infection [1,2].

A recent study compared antibody levels between age groups and reported lower levels of spike-specific, and especially neutralising antibodies, in the older adults (over the age of 80) compared to younger individuals after vaccination with Comirnaty® (Pfizer-BioNTech) [3]. This suggests that older adults may have a weaker immune response to the vaccine and thus a faster antibody decline, which has been underlined in a cohort of 3808 health care workers in Israel, showing a substantially lower rate of IgG antibodies in those aged 65 or older compared to those 18 to less than 45 years of age, six months after receiving the second dose of the Comirnaty® (Pfizer-BioNTech) vaccine [4].

However, it is still not known what antibody levels are needed to protect from severe, symptomatic disease or infection with SARS-CoV-2. Additionally, these studies did not consider the impact of vaccine generated memory cells on the duration of protective immunity.

The efficacy of the Spikevax® vaccine (Moderna) against COVID-19 and severe COVID-19 has been showed to be maintained for more than 5 months after the second dose among all subgroups, including those at risk for severe complications [5]. Nonetheless, in these trials, the vaccine effectiveness was not reported after 5 months and impact of SARS-CoV-2 VOC was not assessed, since circulation of the variants was low.

The recently published data from the original randomised controlled clinical trial of Comirnaty® (Pfizer-BioNTech) confirmed that the vaccine effectiveness against laboratory-confirmed COVID-19 remained high for up to six months after receiving the primary vaccination series (*i.e.*, two-dose vaccine scheme). Nevertheless, a gradual decline was observed from the peak vaccine effectiveness of 96.2% (95% CI: 93.3–98.1) between seven days and two months after the second dose to the period between two months and four months after the second dose (VE = 90.1%; 95% CI: 86.6–92.9), and the period between four months and the data cut-off (vaccine effectiveness = 83.7%; 95% CI: 74.7–89.9) [6].

A test-negative case-control study from England in the general population recently published as a preprint by Public Health England compared the incidence of COVID-19 (560,000 Alpha variant cases, 894,000 Delta variant cases, 21,000 hospitalisations, 4,500 deaths) in 1.5 million vaccinated individuals (Vaxzevria® or Comirnaty®(Pfizer-BioNTech)) *versus* 3.7 million unvaccinated individuals. In this study, >20 weeks after the second dose, the rate of protection against COVID-19 (symptomatic and asymptomatic)

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had significantly decreased (compared to protection rates from phase III trials): 47.3% (CI 95%: 45.0–49.6) for Vaxzevria® (AstraZeneca-Oxford University) and 69.7% (68.7–70.5) for Comirnaty® (Pfizer-BioNTech). Importantly, this decrease was not show in COVID-19-related hospitalisation: 77% (70.3–82.3) for Vaxzevria® and 92.7% (90.3–94.6) for Comirnaty® (Pfizer-BioNTech); and COVID-19 related-death: 78.7% (52.7–90.4) for Vaxzevria® (AstraZeneca-Oxford University) and 90.4% (85.1–93.8) for Comirnaty® (Pfizer-BioNTech), respectively.

These results have been confirmed by two other large studies in Qatar [7] and in the USA [8].

Furthermore, the currently dominant Delta VOC, associated with higher transmissibility, exposure to higher viral loads, as well as partial escape from cellular and humoral responses can have a negative impact on protective immunity. The same data from Public Health England confirmed the decreased effectiveness following two doses of Vaxzevria® (AstraZeneca-Oxford University) or Comirnaty® (Pfizer-BioNTech) against Delta VOC compared to the Alpha VOC-related infections more marked with Vaxzevria® (AstraZeneca-Oxford University) [9] without real differences between variants on COVID-19-related hospitalisations and deaths [10].

Effectiveness of the booster dose

First immunological data showed that a booster shot of ARNm vaccine induced substantially higher neutralising antibody titres against the wild type SARS-CoV-2 virus as well as Beta and Delta variants, compared to levels reported after the second dose of vaccine. Indeed, neutralisation Geometric Mean titres following dose 3 of Comirnaty® (Pfizer-BioNTech) vaccine increased to more than 5 times as high (in 18-to-55-year-olds) and to more than 7 times as high (in 65-to-85-year-olds) against wild-type virus, more than 15 times as high (in 18-to-55-year-olds) and to more than 20 times as high (in 65-to-85-year-olds) against Beta variants and more than 5 times as high (in 18-to-55-year-olds) and to more than 12 times as high (in 65-to-85-year-olds) against Delta variants [11]. Similarly, data on Spikevax® (Moderna) showed that a booster dose increased neutralisation titres against wild-type variants (3.8 times), beta variants (32 times) and delta variant (42 times) compared to post dose 2 titres [12].

To date, there are no data from randomised controlled trial on booster doses effectiveness. However, first real-life effectiveness data from Israel compared the occurrence of COVID-19 and severe COVID-19 in a booster group (at least 12 days after Comirnaty® (Pfizer-BioNTech) dose 3) and a non-booster group in a large study including 1.14 million people aged 60 years and older at least 5 months after dose 2. The rate of confirmed infection was lower in the booster group than in the non-booster group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3) and the rate of severe COVID-19 was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). Adverse events after booster dose were similar to those after dose 2. According to these data, the booster dose might prevent 86.6 all forms of infection per 100,000 patients and 7.5 severe forms per 100,000 patients [13]. These data suggest that the additional protection afforded by the booster dose is therefore considerably greater against mild to moderate forms than against severe forms.

In conclusion, the decrease in vaccine protection over time appears to be real for all forms of infection starting from the 6th month after the second injection, but does not appear to have a real impact on the risk of COVID-19-related hospitalisation or death. The decrease in protection is more pronounced in people older than 65 years and in those at higher risk of severe COVID-19. The usefulness of a booster dose is still debated but is recommended in a growing number of countries in the elderly, those at higher risk of

Table 1

	2 weeks to 2 months efficacy against COVID-19** (Wild type strains)	> 4 months efficacy* (Wild Type strain)		> 5 months effectiveness** (Delta variant)		Fold of increase in neutralising antibody titre after the receipt of a booster dose at Month 6***		
		COVID-19	*COVID-19-related hospitalisation*	*COVID-19*	*COVID-19 related-hospitalisation*	Wild Type	Beta	Delta
Comirnaty® (Pfizer-BioNTech	96.2% (95%CI [93.3–98.1])	83.7% [74.7–89.9]	96.7% [80.3–99.9]	69.7% [68.7–70.5]	92.7% [90.3–94.6]	5 (18–55 years old) 7 (65–85 years old)	15 (18–55 years old) 20 (65–85 years old)	5 (18–55 years old) 12 (65–85 years old)
Spikevax® (Moderna)	91.8% [86.9-95.1]	92.4% [84.3-96.8]	98.2% [92.8–99.6]	Not available		3.8#	32#	42#
Vaxzevria® (AstraZeneca-Oxford University)	74.0% [65.3–80.5]	Not available		47.3% [45.0-49.6]	77.0% [70.3-82.3]	Not available		
Covid-19 Vaccine Janssen®, Janssen-Cilag	66.1% [55.0–74.8]	Not available		Not available		Not available		

##Data not published.
* After the receipt of Dose 2, data from randomised controlled trials.
** After the receipt of Dose 2, data from "real-life" cohorts.
*** Compared to neutralising antibody level after Dose 2.
# Booster dose was half the dosage of D1/D2.

exposition or to contract severe forms. Upcoming data on vaccine duration of protection and real-life efficacy and safety of booster doses will add evidence on its hypothetical interest in the general population. Finally, it must be underlined that the priority should remain to vaccinate all eligible individuals not yet vaccinated with the recommended dose regimen (Table 1).

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Declaration of Competing interests

Other authors do no report competing interest.

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