VACCINE EFFECTIVENESS OF THE SECOND AND THIRD COVID-19 BOOSTERS IN BELGIUM

(ADMINISTERED DURING 2022 AUTUMN CAMPAIGN)

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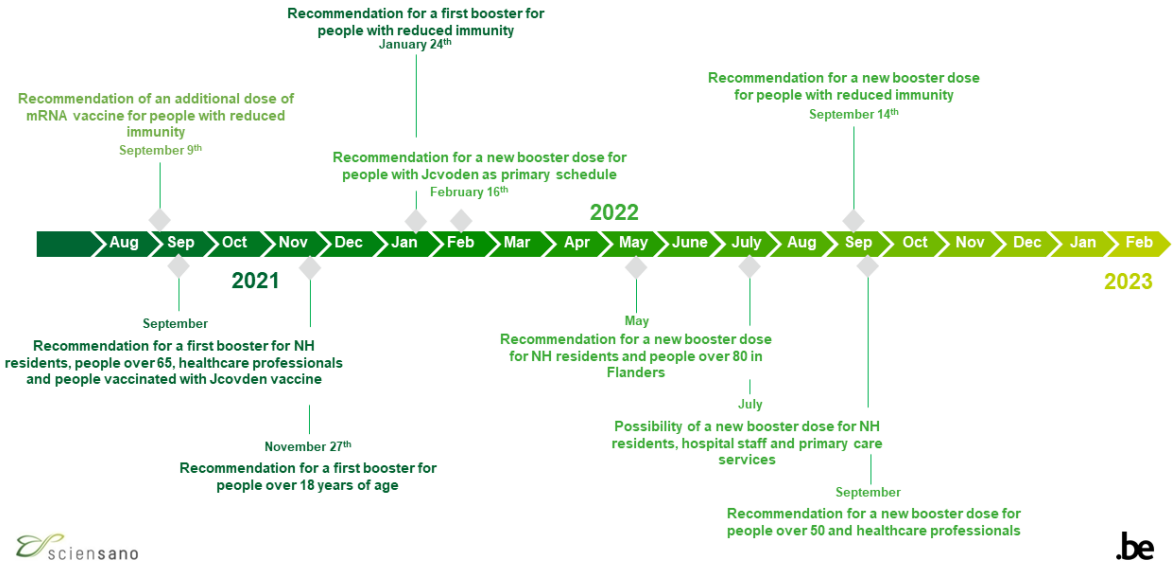
1. Context

In early 2021, the primary vaccination campaign against COVID-19 was rolled out to the adult population in Belgium, followed by the first booster campaign towards the end of the year. At the beginning of 2022, booster doses were recommended and offered to people meeting the definition of immunocompromised conditions (from January 24, 2022)[1] and to people who had received the Jcovden vaccine (Johnson&Johnson®) as a primary COVID-19 vaccination schedule (from February 16, 2022)[2]. From May 2022, Flanders offered a second booster vaccination to nursing home (NH) residents and people aged over 80 years. In early July 2022, a second booster vaccination was offered to people working in the healthcare sector and those living in nursing homes in all regions of Belgium[3] (**Figure 1**).

Figure 1. *Chronology of recommendations by the Interministerial Conference for the COVID-19 vaccination campaign in Belgium, 2021-2023.*



[1] Booster dose for those with weakened immunity - IMC Public Health | FPS Public Health (belgium.be)
[2] Booster dose for those with Jcovden as a primary COVID-19 vaccination schedule - IMC Public Health | FPS Public Health (belgium.be)
[3] IMC communication on the 6th of July 2022 - IMC Public Health | FPS Public Health (belgium.be)

From the 12th of September 2022 onwards, the Interministerial Conference (IMC) organised an autumn vaccination campaign with a systematic invitation for a new booster dose, consecutively for immunocompromised people, people aged over 65 years, healthcare workers and people aged between 50 and 64 years. People aged 18-49 years were allowed to receive a booster dose as well but were not systematically invited. People who had already had a booster dose earlier in the year were also eligible to receive a subsequent (third) booster during this new campaign, with a minimum interval of 3 months between the 2 doses. As such, this autumn campaign included mainly administrations of second, but also third booster doses.

Here we assessed the COVID-19 vaccine effectiveness against symptomatic infection and hospital admission among those who received the second and third boosters in Belgium administered during and following the autumn vaccination campaign of 2022, compared to those who did not receive a vaccine during this time.

2. Methodology

Booster vaccination is mainly provided by mRNA vaccines (Comirnaty-Pfizer® and Spikevax-Moderna®). Although other types of vaccines have gradually been used as boosters, their share of the total booster distribution is very low[4]. The booster vaccination campaigns used the original version of COVID-19 vaccines until September 2022 when the bivalent formulations were put into use, targeting specific Omicron sub-variants (BA.1 sub-variant with Comirnaty® Omicron BA.1 and Spikevax® Omicron BA.1 vaccines, and BA.4 and 5 sub-variants with Comirnaty® Omicron BA.4-5) combined with the original SARS-CoV-2 strains. As our study group consists of individuals who received their second or third booster dose from the 12th of September 2022 onwards, we consider that almost all of them will have been administered a bivalent vaccine. In this study, no distinction has been made regarding brands of primary vaccination, brands of booster(s) vaccination, and the bivalent formulations for the second or third booster. Also, no distinction has been made by Omicron sub-variants[5].

Vaccine effectiveness (VE) was defined as the percentage reduction in the average risk of COVID-19 infection or hospital admission due to COVID-19[6] among vaccine recipients, as compared with a control or reference population, and estimated by using a test-negative study design (case and control model)[7]. COVID-19 VE studies mostly used the *unvaccinated* population (sometimes taking into account previous infection status) as the reference group, allowing the estimation of the direct effect of the vaccination. However, this group has become less suitable for our objective, because of the small number of persons remaining unvaccinated, particularly in the older age group (65 years and over), possibly complicating comparisons. Instead, it has become more relevant to assess the effectiveness of a new COVID-19 vaccination compared to a population that includes also those who received their last COVID-19 vaccine a specific time ago. For this report, we consider individuals who have not received a dose of COVID-19 vaccine since March 2022 as the reference group, as this date roughly marks the end of the first booster campaign. The risk of symptomatic infection and hospitalization was compared between persons who received their last COVID-19 vaccine after the 12th of September 2022 and those who had not received a COVID-19 vaccine dose since March 2022. People who received a COVID-19 booster dose between March 2022 and the 11th of September 2022 were excluded. This study includes all cases from the 12th of September 2022 until the 12th of April 2023. Cases and hospitalizations were defined, respectively, as individuals with at least one positive test and matching symptoms for SARS-CoV-2 and hospital admissions linked to COVID-19 symptoms within 4 weeks following a positive test with matching symptoms for SARS-CoV-2.

Within the period in which Belgian individuals received their second or third booster dose, there were different contextual circumstances, such as circulating variants of concern with different characteristics, varying numbers of infections and hospitalizations, etc. To limit the bias related to these different elements, an adjustment for the calendar week in which the test (Polymerase Chain Reaction, Antigenic or Rapid Antigenic tests) was performed has been included in the model. Also, other potential confounders have been taken into account. While age remains the strongest risk factor for severe COVID-19 outcomes, we also adjusted for underlying health conditions in line with the different vaccination recommendations made by the Superior Health Council of Belgium (SHC). A 3-categories classification (having immunocompromised conditions, having other underlying conditions associated with an increased risk of severe COVID-19, or having none) has been included in the model. This study also adjusted for having tested positive for COVID-19 previously, as a

[4] COVID-19 Weekly report – Sciensano (NL and FR)

[5] Only a small fraction of COVID-19 samples variants were analysed and determined during this period. There has not been one single dominant variant or sub-variant (prevalence of >80% in the COVID-19 laboratory tests) since the start of the second booster vaccination campaign. Belgium COVID-19 Dashboard - Variants - Sciensano

[6] To estimate the VE in preventing hospitalization following a symptomatic infection, we assessed whether people with a symptomatic infection were hospitalized in the 4 weeks following a COVID-19 infection. The Hazard ratio of hospitalization following a symptomatic infection was calculated for each vaccination status using a Cox regression model.

[7] The detailed methodology used for this COVID-19 vaccine effectiveness study is described in a published article : Braeye T, van Loenhout JAF, Brondeel R, Stouten V, Hubin P, Billuart M, Chung PYJ, Vandromme M, Wyndham-Thomas C, Blot K, Catteau L. *COVID-19 vaccine effectiveness against symptomatic infection and hospitalisation in Belgium, July 2021 to May 2022.* Euro Surveillance. 2023 Jun;28(26):2200768. doi: 10.2807/1560-7917.

higher protective effect against infection has been observed in people vaccinated who had at least one notified previous COVID-19 infection compared to those without[4]. Finally, the model was adjusted for the person's sex, the province of residence, and whether the person lives in a collective household (as a proxy for nursing home residents, which is a particularly vulnerable population).

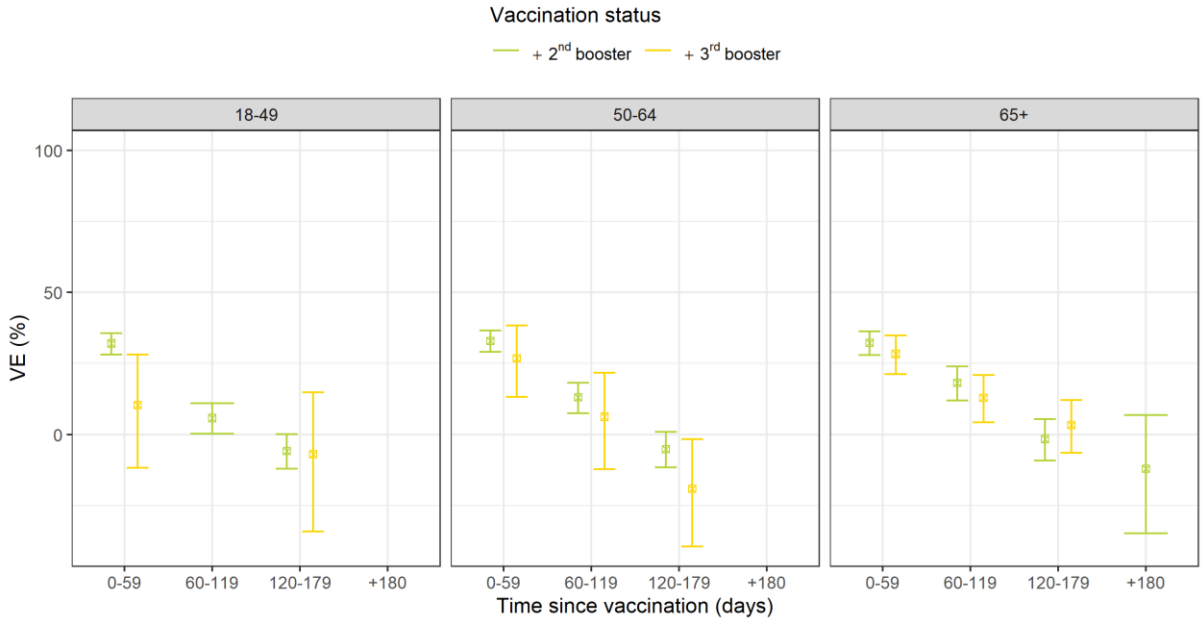
3. Vaccine effectiveness of the second and third boosters

By the 12th of April 2023, 41,3% (3 863 671) of the Belgian adult population received a second booster and 5,2% (488 040) a third booster dose. From the 12th of September 2022 until the 12th of April 2023, 34,4% (3 220 401) of the Belgian adult population has received a second booster, concerning 49,8% of the population aged 50 and over and 53,6% of the population aged 65 and over. During the same period, 5,2% (485 442) of the Belgian adult population received a third booster, concerning 9,6% of the population aged 50 and over and 16,2% of the population aged 65 and over. The majority of the third-time-boosted population could be characterized as being more at risk of severe COVID-19 due to frailty because of an older age or having underlying medical conditions associated with a higher risk of severe COVID-19 outcomes.

3.1. VACCINE EFFECTIVENESS AGAINST SYMPTOMATIC COVID-19 INFECTION

Figure 2 shows the estimates of COVID-19 VE of a second and third booster against symptomatic infection, by age group, in Belgium. The reference group consists of people not having received a vaccine dose since March 2022.

Figure 2. *Relative vaccine effectiveness against COVID-19 symptomatic infection, by age group and vaccination status, in Belgium from the 12th of September 2022 to the 12th of April 2023.*



The vertical lines around each point on the graph represent the 95% confidence interval. The narrower the interval, the more precise the estimate of vaccine effectiveness. VE estimates are not shown when the width of their confidence interval exceeds 50%. The time since vaccination corresponds to the day the vaccination is considered to be effective[8].

The initial protection against symptomatic infection of a second booster is estimated at 32,0% among the 18-49 year-olds, 32,9% among 50-64 year-olds and 32,2% among those aged 65 years and over. For the third booster, the initial level of protection is evaluated at 10,3% among the 18-49 year-olds, 26,9% among 50-64 year-olds and 28,3% among those aged 65 and over.

Over time, the vaccine protection decreases at a comparable rate for the second and third booster. The decline in VE appears, however, to be slightly slower in the 65+ years age group, compared to the 18-49 and the 50-

[8] Booster doses were considered effective 7 days after administration in case of a monovalent COVID-19 vaccine dose and 14 days for a COVID-19 bivalent vaccine dose.

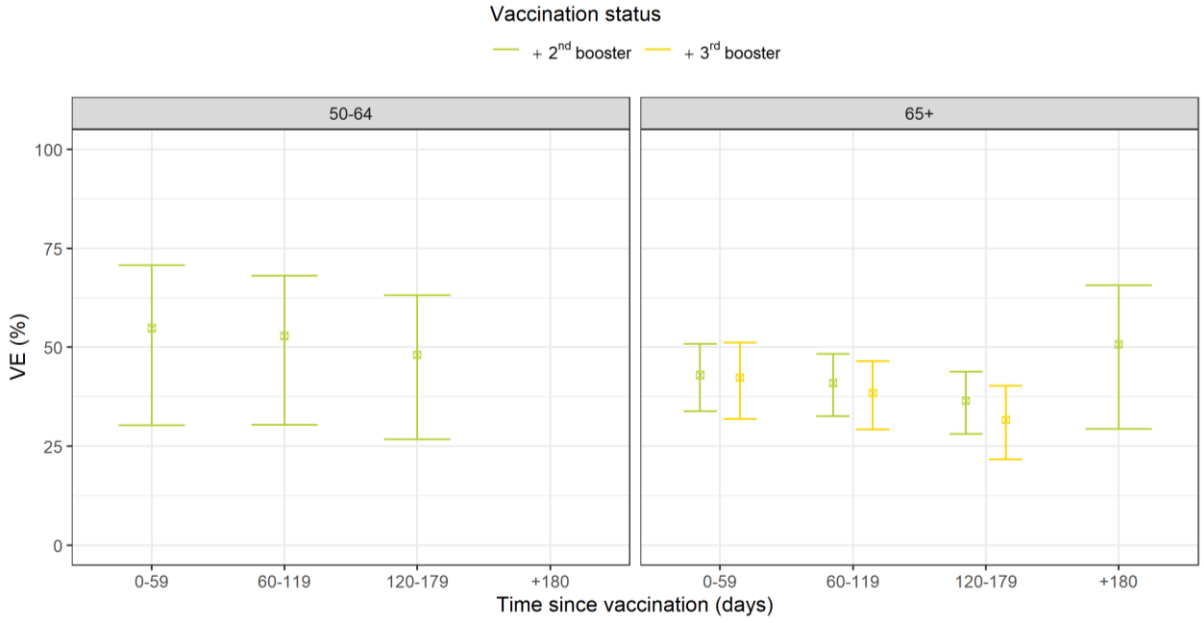
64 years age groups. The administration of a third booster dose seemed to restore the protection offered by the vaccine to an equivalent level as the second dose, with the exception of the 18-49 years age group where the initial protection level was markedly lower for the third booster. However, VE estimates for the third booster show wide confidence intervals, implying a higher uncertainty of the estimates, especially for the age groups younger than 65 years, probably due to the low number of individuals having received a third booster among those age groups.

For all adult age groups, the additional protection against COVID-19 symptomatic infection provided by the second and third booster can no longer be observed after 120 days.

3.2. VACCINE EFFECTIVENESS AGAINST HOSPITALISATION DUE TO COVID-19

Figure 3 presents the VE of a second and third booster against hospitalisation due to COVID-19, following a symptomatic infection, by age group, in Belgium. The reference group consists of people not having received a vaccine dose since March 2022.

Figure 3. *Relative vaccine effectiveness against hospitalisation due to COVID-19, by age group and vaccination status, in Belgium from the 12th of September 2022 to the 12th of April 2023.*



The vertical lines above and beneath each point on the graph represent the 95% confidence interval. The narrower the interval, the more precise the estimate of vaccine efficacy VE estimates are not shown when the width of their confidence interval exceeds 50%.
The time since vaccination corresponds to the day the vaccination is considered to be effective[9].

The initial protection offered by a second booster against hospitalisation among 50-64 year olds is estimated at 54,8% and remains rather stable over time, i.e. at 120 to 179 days after administration of the second booster, the vaccine protection is evaluated at 48,1%. However, the confidence intervals of the VE estimates for the 50-64 year olds are quite wide, due to the relatively low number of hospitalisations among this age group that were registered within the study period. Accurate estimates for those who received the third booster could not be calculated for this age group, also due to the low number of registered hospitalizations among persons with this vaccine status and within this age group. For the same reason, the 18-49 year olds are not presented either.

For those aged 65 years and over, the initial protection provided by the second and third booster were 43,0% and 42,4%, respectively, while the level of protection more than 120 days after vaccination was estimated at

[9] Booster doses were considered effective 7 days after administration in case of a monovalent COVID-19 vaccine dose and 14 days for a COVID-19 bivalent vaccine dose.

36,5% for the second booster and 31,7% for the third booster, and thus appears remaining relatively stable over time. Administration of a third booster dose recovered the waned protection level after the second booster.

VE estimates regarding ICU admissions among the adult population could not be evaluated due to the low number of events registered during this time period.

4. Conclusion

Administration of a second or third booster has shown a moderate protective effect against a symptomatic infection caused by COVID-19 in the adult population. Second and third COVID-19 booster vaccinations were more effective in protecting individuals against hospitalization, and this additional protection remained rather stable over time in the age group described as most at risk (50 years and over age categories).

Vaccine effectiveness offered by the first booster doses was previously estimated at 52,1% against symptomatic infections and 79,6% against hospitalization following symptomatic infection due to COVID-19 for the 65 years and over age group, compared to unvaccinated persons[10]. However, these estimates cannot be compared for several reasons. Firstly, a different reference group was used consisting of unvaccinated persons, which inevitably leads to higher estimates of effect, than using a reference group in which a large share was vaccinated with a primary schedule and first booster (limited added effect). Secondly, the dominant variants circulating during the first booster campaign and those circulating during the second/third booster campaigns differ in terms of transmissibility, degree of pathogenicity and virulence, and immune escape characteristics, not allowing a direct comparison between the vaccine effectiveness of the 2 different vaccines. It should also be noted that between the first and second/third booster doses, a relatively large number of COVID-19 infections were not documented, due to a shift toward a non-systematic testing strategy. Consequently, the protection related to previous infections during the first wave of Omicron has been underestimated in our study, resulting in a bias for the difference between recently vaccinated and not recently vaccinated individuals.

Another point to be raised when reading our results is to take into account the vaccines used and the viral context of the period studied. Adapted vaccines were developed because of the immune escape associated with the Omicron variants. The BA.1-adapted vaccines were introduced in Belgium in mid-September, followed shortly afterwards by the BA.4/5 formulation in early October 2022. At the same time, Omicron BA.5 and BA.4 and their sub-variants accounted for 92% and 6% respectively of the variants identified among COVID-19 cases in Belgium, while Omicron BA.1 was last detected in Belgium in May 2022. 2 months after the start of the autumn vaccination campaign, on November 12, 2022, Omicron BA.1-adapted vaccines accounted for 71% of all vaccines administered as a second booster in Belgium, while Omicron BA.4/5-adapted vaccine accounted for 9%. In mid-February 2023, new BA.2 variants and sub-variants appeared and represented 86% of variants identified among COVID-19 cases in April 2023, while Omicron BA.5 and its sub-variants accounted for 3%, and Omicron BA.4 has not been detected in Belgium since December 2022[11].

The next COVID-19 revaccination campaign will probably be held in autumn 2023 in Belgium. Following the latest recommendations of the European Centre for Disease preventions and Control (ECDC) and the European Medical Agency (EMA), published in a joined statement[12], this campaign is expected to involve newly adapted monovalent COVID-19 vaccines based on the variants that were most present in June 2023 (Omicron sub-variants XBB1.5 or XBB1.16). These adapted vaccines could provide better protection against current variants and target potentially newly emerging strains.

[10] COVID-19 Weekly report – Sciensano (NL and FR)
[11] Belgium COVID-19 Dashboard - Variants - Sciensano
[12] ECDC-EMA statement on updating COVID-19 vaccines composition for new SARS-CoV-2 virus variants (europa.eu)