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Performance comparison between heterologous and homologous COVID19 vaccine schedules on Omicron variant incidence: A real-world retrospective cohort study in Southern Italy

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ABSTRACT

As the COVID19 pandemic progresses, there is an increasing need to evaluate the performance of vaccine strategies. This study investigated the vaccine schedule performance of heterologous vaccination compared to homologous vaccination in preventing Omicron SARS-CoV2 infection in the adult population.

This retrospective cohort study utilized data from the Infections Regional Information System and the Apulia Regional Vaccine Registry to identify individuals who received a booster dose of one of 14 different COVID19 vaccination schedules between September 2021 and August 2022 in the province of Lecce, Southern Italy. The standardized cumulative incidence of SARS-CoV2 infection after the booster dose was assessed and the risk of infection between subgroups of heterologous and homologous vaccination schedules was compared using the Cochran-Mantel-Haenszel test.

A total of 469,069 subjects were included in the study. The standardized incidence of SARS-CoV2 infection varied greatly among different vaccine schedules, with the highest and lowest being AZ-AZ-BNT (34.7 %) and MOD-MOD-BNT (18.9 %), respectively, and some heterologous schedules performing better than homologous ones.

The risk of SARS-CoV2 infection was significantly lower in individuals who received specific heterologous vaccination schedules compared to homologous vaccination schedules, the best performing being MOD-MOD-BNT with a common odd ratio of 0.661 (IC. 95 % [0.620–0.704]).

This study provides evidence that heterologous vaccination schedules may be more effective in preventing Omicron SARS-CoV2 infection compared to homologous vaccination schedules, highlighting how the vaccine product, rather than the platform, is involved in the different protection provided by heterologous vaccination.

1. Introduction

The SARS-CoV2 virus was first detected in Italy in January 2020. The first outbreak was recorded in late February 2020 and the first deaths resulting from infection were also observed. On March 11, 2020, the World Health Organization (WHO) declared the new disease known as COVID19 a "pandemic" due to its global distribution [1].

In 2020, the total number of deaths in Italy was the highest recorded since the end of World War II; in 2021, the total number of deaths was less than 2020, but still higher than the average for the period 2015–2019. The majority of the excess mortality in 2021 was observed in the first quarter and was largely due to the increased mortality observed in the central-southern regions, which were predominantly affected by the COVID19 pandemic starting in October 2020, with the beginning of the second pandemic wave [2].

December 27, 2020, the so-called "Vaccine Day," marked the official start of the COVID19 vaccination campaign throughout Europe. Vaccinations had a global impact, preventing 14.4 million deaths from COVID19 in 185 countries in the first year of the vaccination campaign [3].

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Table 1
Vaccine schedules for COVID19 vaccination. The table presents the 14 schedules authorized by the Italian Ministry of Health during the study period. In the first column there is the number of the schedule. In the second column each schedule is represented by the abbreviation of the vaccines used (BNT, MOD, JNJ, AZ, NVX) following the order of administration. In the "product based" column the schedule is described differentiating for each single product available. In the "platform based" column each schedule is synthesized according to the type of vaccine used regardless of the commercial product.

n°	Vaccine Schedule (abbreviation)	Vaccine Schedule (product based)	Vaccine Schedule (platform based)
1	BNT-BNT-BNT	Homologous prime-boost Pfizer Comirnaty	Homologous prime-boost mRNA vaccines
2	MOD-MOD-MOD	Homologous prime-boost Spikevax Moderna	
3	MOD-MOD-BNT	Heterologous prime-boost BNT after MOD	Heterologous prime-boost mRNA vaccines
4	BNT-BNT-MOD	Heterologous prime-boost MOD after BNT	
5	JNJ-BNT	Heterologous prime-boost BNT after JNJ	Heterologous prime-boost with mRNA vaccine after viral vector vaccines
6	JNJ-MOD	Heterologous prime-boost MOD after JNJ	
7	AZ-AZ-BNT	Heterologous prime-boost BNT after AZ	
8	AZ-AZ-MOD	Heterologous prime-boost MOD after AZ	
9	AZ-BNT-BNT	Heterologous prime BNT after AZ	Heterologous prime with mRNA vaccine after viral vector vaccine
10	AZ-MOD-MOD	Heterologous prime MOD after AZ	
11	AZ-BNT-MOD	Heterologous prime-boost MOD after heterologous prime BNT after AZ	Heterologous prime with mRNA vaccine after viral vector vaccine and heterologous booster with different mRNA vaccines
12	AZ-MOD-BNT	Prime-boost heterologous BNT after heterologous prime MOD after AZ	
13	NVX-NVX-BNT	Heterologous prime-boost BNT after NVX	Heterologous prime-boost mRNA vaccine after recombinant adjuvanted vaccine
14	NVX-NVX-MOD	Heterologous prime-boost MOD after NVX	

In Italy, 5 different COVID19 vaccines have been authorized for the primary vaccination cycle:

a) Comirnaty by Pfizer-BioNTech (BNT) authorized on December 21, 2020, by the European Medicines Agency (EMA) and on December 22, 2020, by the Italian Medicines Agency (AIFA) with two doses 21–40 days apart.
b) Moderna's Spikevax (MOD) vaccine authorized by EMA on January 6, 2021 and on January 7, 2021, by AIFA with two doses 28–40 days apart.
c) AstraZeneca's Vaxzevria (AZ) vaccine: authorized by EMA on January 29, 2021 and on January 30, 2021, by AIFA with two doses 4–12 weeks apart.
d) Johnson & Johnson's Janssen (JNJ) vaccine authorized on March 11, 2021 by EMA and on March 12, 2021, by AIFA with a single dose.
e) Novavax's Nuvaxovid (NVX) vaccine authorized on December 20, 2021, by EMA and on December 22, 2021 by AIFA with two doses 21 days apart.

In the autumn of 2021, considering the increase in cases and the epidemiological trend of the infection, following a positive opinion from AIFA, the Ministry of Health approved the administration of a "booster" dose, intended as a single dose of COVID19 vaccine at a distance from the primary vaccination cycle [4].

The administration of the first booster dose (also called the third dose) was recommended starting from September 27, 2021, for the most vulnerable populations (over 80, residents and employees of nursing homes, people with comorbidities), and then extended on October 8, 2021, to other groups, including healthcare workers, people over 60, and at risk individuals over 18. Using as boosters firstly the Comirnaty Pfizer BNT162b2 30 μg and later the Spikevax Moderna mRNA-1273, at a new dosage of 50 μg in 0.25 mL, approved on October 29, 2021.

During the initial phase of booster doses planning, the recommended minimum interval between the end of the primary cycle and the actual administration of the dose was 6 months (180 days).

On November 22, 2021, the time interval between the primary cycle and the booster dose was reduced to 5 months (150 days) and from November 25, 2021, the administration of the booster dose has been recommended for all individuals over 18. On December 24, 2021, the recommendation was extended to individuals over 16, and in the 12–15 age range for vulnerable individuals, with the time interval reduced to 4

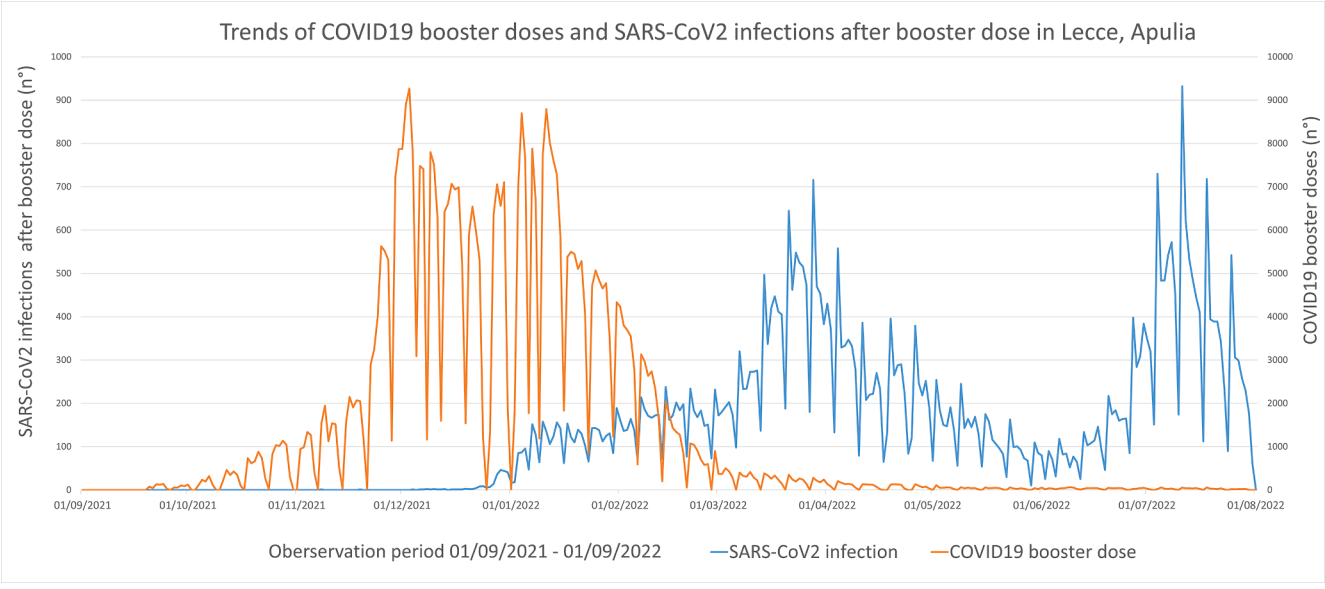

Fig. 1. Number of COVID19 vaccine booster doses administered by date (scale on the right) and the number of SARS-CoV2 infections by date (scale on the left) to the cohort of individuals included into the study during the observation period (01/09/2021–01/08/2022).

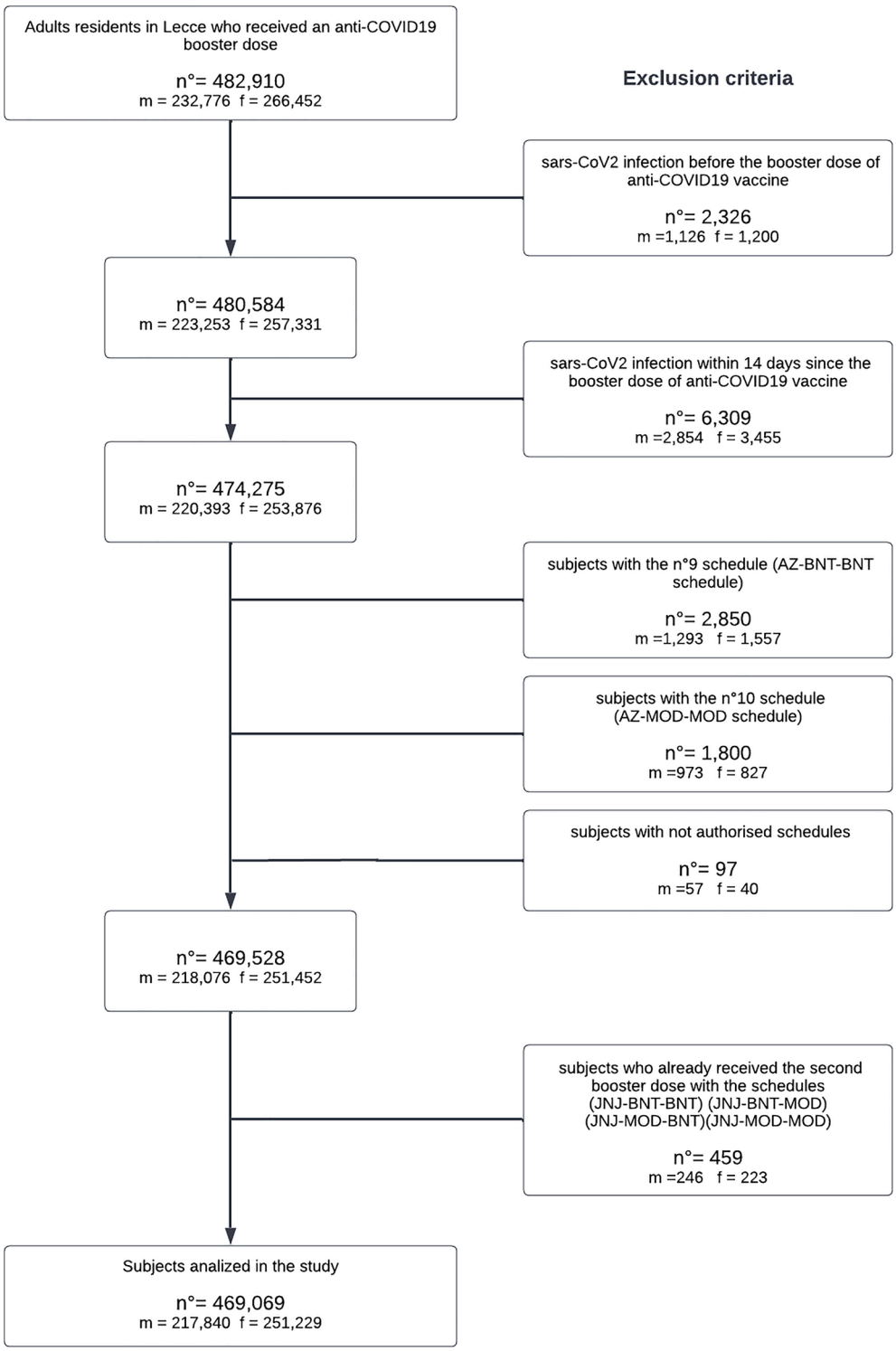

Fig. 2. The flowchart displays the number of individuals included and excluded into the study detailing how many individuals were excluded according to each exclusion criteria, as described in Section 2.4.

months (120 days). The only vaccine approved for the booster dose in individuals under 18 is Comirnaty Pfizer BNT162b2 30 µg, regardless of the type of vaccine used for the primary cycle [5].

On April 8, 2022, the administration of the second booster dose (second booster) began.

No specific recommendations regarding which COVID19 vaccine product/brand to use for the booster regimen was issued by the Ministry of Health. This decision aimed to promote organizational flexibility and simplify vaccine procurement, in order to counter the exponential increase of cases due to the combined effect of virus mutation and the decline in immunity resulting from the primary cycle [6], effectively opening up to heterologous vaccination (mix & match), previously authorized exclusively for the AZ vaccine [7].

This startegy was supported by the scientific evidence regarding the safety of heterologous vaccination and the comparable reactogenicity [8], taking into account the possibility that the mix & match strategy

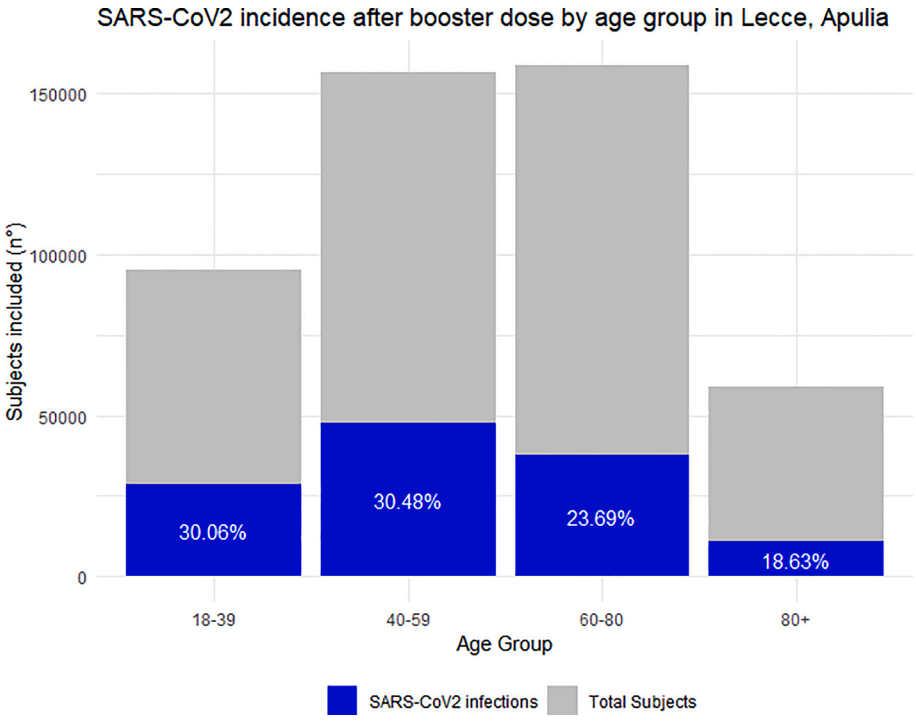

Fig. 3. The histogram displays the observed incidence of SARS-CoV2 infections after the administration of the COVID19 vaccine booster dose stratified by age group during the observation period 01/09/2021–01/08/2022 in the study population.

Table 2
Number of individuals included into the study for each schedule (with the percentage of each schedule over the total) and the standardized incidence of SARS-CoV2 infections after the administration of the COVID19 vaccine booster dose during the observation period 01/09/2021–01/08/2022. The highest being 34.67 % of schedule 7 (AZ-AZ-BNT) and the lowest schedule 3 (MOD-MOD-BNT).

Vaccine schedule	n° of individuals included (% of total)	Standardized incidence of SARS-CoV2 infections
1 BNT-BNT-BNT	236,962 (50.52 %)	28.69 %
2 MOD-MOD-MOD	50,165 (10.69 %)	20.50 %
3 MOD-MOD-BNT	6,207 (1.32 %)	18.93 %
4 BNT-BNT-MOD	87,696 (18.69 %)	23.09 %
5 JNJ-BNT	8,830 (1.88 %)	25.59 %
6 JNJ-MOD	11,294 (2.41 %)	22.64 %
7 AZ-AZ-BNT	18,074 (3.85 %)	34.67 %
8 AZ-AZ-MOD	49,285 (10.51 %)	33.41 %
11 AZ-BNT-MOD	452 (0.09 %)	26.62 %
12 AZ-MOD-BNT	104 (0.02 %)	25.71 %

may be more effective than homologous vaccination, based on studies on antibody titles (Ig-G anti-spike) [9,10].

COVID19 vaccines provide protection against severe disease and death, but more evidence is needed to determine exactly how well they prevent the infection and transmission of SARS-CoV2 [11].

Despite many studies exploring the vaccination against Omicron variant focusing on the antibody levels and neutralization activity following homologous and heterologous booster vaccination [12], there are only a few studies assessing the real-world vaccine effectiveness [13], and it's still unclear which immunization schedule has a better performance in preventing SARS-CoV2 Omicron variant infection.

1.1. Purpose of the study

The purpose of our study is to investigate the performance of different COVID19 vaccine schedules in preventing SARS-CoV2 Omicron variant infection using real-world data.

Specifically, we aim to answer the question: is COVID19 vaccination with a mix-and-match strategy (heterologous), with regard to the booster dose in adults, more effective in preventing SARS-CoV2 infection than homologous vaccination?

2. Methods

A retrospective cohort observational study was conducted on individuals residing in the province of Lecce (775,348 inhabitants, 19.8 % of the Apulia region population and 1.3 % of the Italian population), linking data on COVID19 vaccinations in the Apulia Region vaccination registry (GIAVA 6.0) with data on SARS-CoV2 infections from the Infections Regional Information System (IRIS).

2.1. Description of data collected from the Infections Regional Information system (IRIS)

Data on confirmed SARS-CoV2 cases were extracted from the regional computerized system "Infections Regional Information System" (IRIS). The platform, available to support the activities of the Regional Health Service Companies and Professionals, was created with the aim of constituting a single point of registration for confirmed cases of SARS-CoV2 infection, with the possibility of following their evolution according to the definitions established by the Ministry of Health (suspected case, probable case, confirmed case) [14].

2.2. Apulia regional vaccine registry (GIAVA 6.0) description

The GIAVA 6.0 platform allows the registration of COVID19 vaccinations (as well as other vaccines including influenza), implementing the Regional Vaccine Registry (AVR) of the Apulia region in Italy. All vaccines registered in the AVR are then transmitted to the National Vaccine Registry (AVN). The GIAVA platform collects data on the vaccination status, the number of doses received, the vaccine brand and batch, the date of administration, and the demographic information.

Table 3
Results of the CMH test comparing heterologous and homologous COVID19 vaccine schedules over SARS-CoV2 infection risk by vaccine product. Each cell of the table provides the results of a corresponding CMH test. For all the tests conducted, the Alpha (significance level) is set at 0.05, Degrees of Freedom (DF) is 1, the M^2 (Critical value) is 3.841, 'p' refers to the p-value (Two-tailed), 'C. OR' denotes the Common Odds Ratio, and 'IC. 95 %' indicates the Confidence Interval at the 95 % level.

Comparison between COVID19 vaccine schedules by product using the Cochran-Mantel-Haenszel test			
VS	MOD-MOD-MOD	BNT-BNT-BNT	Homologous mRNA vaccine
MOD-MOD-BNT	C. OR 0.923 IC. 95 % [0.864–0.987] p = 0.020; M^2 = 5.542	C. OR 0.615 IC. 95 % [0.577–0.655] p < 0.0001; M^2 = 228.893	C. OR 0.661 IC. 95 % [0.620–0.704] p = <0.0001; M^2 = 165.553
BNT-BNT-MOD	C. OR 1.138 IC. 95 % [1.108–1.169] p < 0.0001; M^2 = 89.549	C. OR 0.754 IC. 95 % [0.741–0.768] p < 0.0001; M^2 = 920.373	C. OR 0.809 IC. 95 % [0.795–0.824] p < 0.0001; M^2 = 542.933
JNJ-BNT	C. OR 1.396 IC. 95 % [1.318–1.480] p < 0.0001; M^2 = 127.501	C. OR 0.880 IC. 95 % [0.838–0.924] p < 0.0001; M^2 = 26.212	C. OR 0.934 IC. 95 % [0.889–0.980] p = <0.006; M^2 = 7.524
JNJ-MOD	C. OR 1.120 IC. 95 % [1.062–1.181] p < 0.0001; M^2 = 17.379	C. OR 0.717 IC. 95 % [0.685–0.750] p < 0.0001; M^2 = 206.836	C. OR 0.765 IC. 95 % [0.731–0.801] p < 0.0001; M^2 = 134.609
AZ-AZ-BNT	C. OR 2.045 IC. 95 % [1.957–2.138] p < 0.0001; M^2 = 1041.372	C. OR 1.216 IC. 95 % [1.176–1.257] p < 0.0001; M^2 = 132.629	C. OR 1.286 IC. 95 % [1.244–1.329] p < 0.0001; M^2 = 222.069
AZ-AZ-MOD	C. OR 1.928 IC. 95 % [1.858–2.001] p < 0.0001; M^2 = 1258.638	C. OR 1.041 IC. 95 % [1.017–1.065] p = 0.001; M^2 = 11.591	C. OR 1.097 IC. 95 % [1.072 -1.122] p < 0.0001; M^2 = 63.512
AZ-BNT-MOD AZ-MOD-BNT	C. OR 1.313 IC. 95 % [1.082–1.594] p = 0.007; M^2 = 7.401	C. OR 0.839 IC. 95 % [0.693–1.016] p = 0.080; M^2 = 3.065	C. OR 0.895 IC. 95 % [0.739–1.083] p = 0.273; M^2 = 1.200

Through GIAVA it is possible to have a view-only access to the AVN, thus only regional data can be exported. GIAVA data are linked with the IRIS system, automatically acquiring data on infections detected in the Apulia region. Infections detected in other regions or foreign states, which would not be available on the IRIS system, can be compiled only manually.

2.3. Definition of SARS-CoV2 infection and vaccination schedules

For each individual, infection was defined as the first laboratory confirmation of SARS-CoV2 by molecular (RT-PCR) or antigen tests available detected through the IRIS system. Considering the authorized COVID19 vaccines and the timing of administration, 14 different vaccination schedules, consisting of a primary cycle and a booster dose, were defined according to the Italian Ministry of Health recommendations and listed in Table 1.

Schedules 9 and 10 (AZ-BNT-BNT and AZ-MOD-MOD) were not included in the subsequent analysis because they do not constitute prime-boost heterologous vaccination but heterologous vaccination in the primary cycle (authorized by the Italian Ministry of Health, following public pressure due to the reported rare but severe adverse effects in subjects vaccinated with AZ) [15].

The cohort was then divided into subgroups according to the type of schedule administered, stratified by sex (male and female) and age groups (<17, 18–39, 40–59, 60–79, >80).

2.4. Inclusion and exclusion criteria

The following are the inclusion and exclusion criteria for subjects in the study:

Inclusion:

- Age over 18 years
- Residence in the province of Lecce, Apulia region, Italy
- "Booster" dose administered in the Apulia region between 01/09/2021 and 01/08/2022
- Primary vaccination administered in the Apulia region.

Exclusion:

- Previous SARS-CoV2 infection before the "booster" dose
- SARS-CoV2 infection within 14 days of the "booster" dose
- Schedules 9 and 10 (AZ-BNT-BNT and AZ-MOD-MOD)
- Subjects without an Italian tax code
- Age under 18 years old
- Immunocompromised individuals that received a booster dose as 4th dose

We excluded individuals with previous SARS-CoV2 infection before the booster dose, because in these individuals immunity is not derived solely from vaccination but also from exposure to the pathogen, their immunity is defined as hybrid. We considered hybrid immunity as a

Table 4
Results of the CMH test comparing heterologous and homologous COVID19 vaccine schedules over SARS-CoV2 infection risk by vaccine platform. Each cell of the table provides the results of a corresponding CMH test. For all the tests conducted, the Alpha (significance level) is set at 0.05, Degrees of Freedom (DF) is 1, the M^2 (Critical value) is 3.841, 'p' refers to the p-value (Two-tailed), 'C. OR' denotes the Common Odds Ratio, and 'IC. 95 %' indicates the Confidence Interval at the 95 % level.

Comparison between anti-COVID19 vaccine schedules by platform using the Cochran-Mantel-Haenszel test	
VS	Homologous mRNA vaccine
Heterologous prime-boost mRNA vaccine	C. OR 0.799 IC. 95 % [0.786–0.813] p < 0.0001; M^2 = 638.868
JNJ-mRNA vaccine	C. OR 0.836 IC. 95 % [0.809–0.865] p < 0.0001; M^2 = 106.399
AZ-AZ-mRNA vaccine	C. OR 1.163 IC. 95 % [1.140–1.186] p < 0.0001; M^2 = 223.268
Heterologous prime-boost with mRNA vaccine after viral vector vaccine	C. OR 1.076 IC. 95 % [1.057–1.096] p < 0.0001; M^2 = 63.593

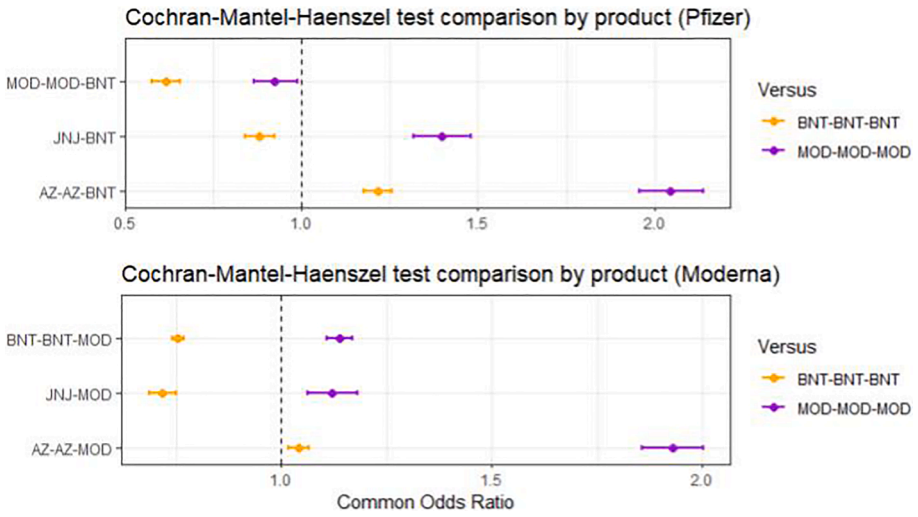

Fig. 4. Results of the CMH test comparing heterologous and homologous COVID19 vaccine schedules over SARS-CoV2 infection risk. In the upper facet are compared the schedules with Comirnaty – Pfizer (BNT) as booster dose, in the bottom facet are compare the schedules with Spikevax – Moderna (MOD) as booster dose. The risk is expressed as a Common Odd Ratio with a 95 % Confidence Interval.

confounding factor and therefore decided to exclude these subjects.

Individuals who contracted SARS-CoV2 infection within 14 days of the booster dose administration were also excluded, as it is known that immunity derived from vaccination has a delayed, rather than immediate, effect due to the activation of memory immune cells [16].

Some immunocompromised patients received an additional dose of vaccine 28 days after the second dose as the conclusion of the primary cycle. Those patients, after completing the primary cycle, received a booster dose that was numerically equivalent to the 4th administration, therefore they were not included in our study.

These geographical criteria were adopted to reduce the possible bias due to the inability to accurately determine the infection and the vaccine schedule in subjects not residing in the Apulia region or without an Italian tax code available. In addition, subjects under 18 years of age were excluded because they are the only category in which the choice of vaccination schedule was not free in terms of "product" and "platform" but was conditioned by the indications of the Italian Ministry of Health [17].

2.5. Statistical analysis

For each individual the time lag between the "booster" dose and the SARS-CoV2 infection was identified with integer numeric values representing the number of days between vaccination and infection. Subjects with values less than 14 were excluded according to the exclusion criteria.

For each schedule the standardized cumulative incidence of SARS-CoV2 infection after booster dose was calculated over the observation period. The standardization was performed utilizing the direct method using the totality of subjects included in the study as standard population adjusting for age class.

The Cochran-Mantel-Haenszel test (hereafter referred to as "CMH test") was used to compare different subgroups of exposure (vaccination schedules defined as heterologous vaccination) to subgroups of non-exposure (2 schedules of homologous vaccination) regarding the binary outcome variable "SARS-CoV2 infection"/"non-infection", after stratifying by sex and age (8 strata), common odds ratios (C. OR) were calculated.

The CMH test allows to analyze the association between a binary predictor or treatment (in this case, the different vaccination schedules) and a binary outcome (in this case, SARS-CoV2 infection) by stratifying the data according to an arbitrary number of categories (4 age groups and 2 sexes in this study) and is based on the M^2 statistic, defined as follows:

$$M^2 = [|\Sigma_k (n_{11k} - n_{1+k}/n_{++k})| - 1/2]^2/[\Sigma_k (n_{1+k}\, n_{2+k}\, n_{+1k}\, n_{+2k})/(n^2_{++k}(n^2_{++k} - 1))]$$

This statistic asymptotically follows a chi-square distribution with 1 degree of freedom. Knowing M^2, we can therefore compute the p-value, and knowing the risk of Type I, alpha, (set to 0.05 in our analysis) we can determine the critical value. The Cramer's V for the individual contingency tables was also analyzed separately from the CMH test to get an idea of their contribution to independence. The tests were conducted using the XLSTAT software (Data Analysis and Statistical Solution for Microsoft Excel, Addinsoft, Paris, France 2017).

3. Results

A total of 482,910 adult subjects (224,379 males and 258,531 females, 74.9 % of adult population of Lecce Province) who received an COVID19 booster vaccination were included in the cohort and were identified from the GIAVA 6.0 and IRIS record linkage [18].

Over 95 % of booster doses were administered between November 2021 and February 2022, while SARS-CoV2 infections were observed from December 2021 to August 2022, as shown in Fig. 1.

A total of 13,841 (2.9 %) subjects were excluded according to the exclusion criteria. In detail, 8,635 (1.8 %) due to the temporal evaluation of the SARS-CoV2 infection and 5,206 (1.1 %) due to the vaccination schedule received, according to the exclusion criteria. Full detail of the inclusion and exclusion criteria applied is available in the flowchart in Fig. 2.

Therefore, the total number of subjects analyzed in the study was 469,069 (217,840 males and 251,229 females), 129,052 (26.72 %) of which contracted SARS-CoV2 infection after booster vaccination (55,376 (24.62 %) males and 73,676 (28.56 %) females). SARS-CoV2 incidence for different age-groups is reported in Fig. 3.

A detailed overview of the total number of subjects included in each vaccination schedule group and SARS-CoV2 incidence stratified by age and sex is provided in Table 1 of the Supplementary materials. Of the identified schedules the most frequent was BNT-BNT-BNT (schedule 1) with 236,962 (50,5 %) subjects included, the second most frequent was BNT-BNT-MOD with 87,696 (18,7 %) subjects. The less frequent schedules were n° 11 and 12 (AZ-BNT-MOD and AZ-MOD-BNT) with only 452 (0.09 %) and 104 (0.02 %) subjects. Schedules including Nuvaxovid (n° 13: NVX-NVX-BNT and n° 14: NVX-NVX-MOD) were not

administered to any subject in our population and could not be analyzed.

3.1. Standardized SARS-CoV2 incidence by vaccine schedule

Overall, 26.61 % of the subjects included in the study had a SARS-CoV2 infection after the booster dose. Analyzing the standardized incidence ratio of COVID19 divided by schedule, the highest ratio (34.67 %) was observed in schedule n° 7 (AZ-AZ-BNT) while the lowest ratio (18.93 %) in schedule n°3 (MOD-MOD-BNT). Full detail of the standardized incidence ratios is available in Table 2.

3.2. SARS-CoV2 infection risk comparison by vaccine schedule

The schedule groups differ widely in size due to the characteristics of the vaccination campaign where the distribution of different products wasn't equal. The association between vaccine schedule and SARS-CoV2 infection after the booster dose is different according to the vaccination schedule. Among the viral vector platform vaccines we observed a statistically significant decreased risk of acquiring SARS-CoV2 for schedules n° 5 and n°6 (JNJ as prime vaccine) in comparison with homologous mRNA vaccination, respectively with a common odd ratio (C.OR) = 0.93 (IC. 95 % [0.889–0.980]) and C. OR = 0.765 (IC. 95 % [0.731–0.801]), even if the comparison with schedule n° 2 (MOD-MOD-MOD) showed an increased risk. Details of the CMH test are shown in Table 3 performing comparisons by vaccine product and in Table 4 by vaccine platform, CMH test results by vaccine product are also displayed in Fig. 4.

Schedules with AZ as prime vaccine resulted having an increased risk of infection compared to any other schedule, with the highest being C. OR = 2.045 (IC. 95 % [1.957–2.138]) for the comparison of schedule n°7 (AZ-AZ-BNT) with schedule n°2 (MOD-MOD-MOD).

Overall, the best performing schedule was the heterologous prime-boost mRNA vaccine schedule n° 3 (MOD-MOD-BNT) with a lower risk compared to any other schedule, as displayed in Fig. 4.

4. Discussion

Our study, based on real-world data from a large cohort in Lecce province, Southern Italy, has confirmed that the protection provided by the COVID19 booster dose is limited to less than a year, as indicated by a 26.72 % incidence of SARS-CoV2 infections following vaccination in the observation time.

According to the 23nd report of "Prevalence and distribution of SARS-CoV2 variants of concern for public health in Italy" elaborated the 2nd of September 2022 through the I-Co-Gen (Italian COVID19 Genomic) and integrated surveillance system of "Istituto Superiore di Sanità" (ISS) [19], which comprehend a prevalence analysis of SARS-CoV2 variants of concern covering the entire observation period of our study, it is possible to state that the Omicron variant was eminently prevalent in Italy in the observation period of the study 01/09/2021–01/08/2022. From the 4th of January 2022 the Omicron variant represented over 90 % of the sequencing in Italy [20], and from the 15th of march 2022 onwards the 99.99 % of the sequencing (more specifically BA.2, 62.8 %; BA.2.9 12.9 %; BA.1.1, 9.5 % and BA.2.3, 5.1 %) [21].

Therefore, it is possible to argue that the incidence of infections that we found is specifically an Omicron SARS-CoV2 incidence, even if we do not have the sequencing specifically performed during our study.

Interestingly, the efficacy of the different vaccination schedules utilized showed a marked variation, with standardized incidence rates of Omicron SARS-CoV2 infections ranging over 10 percentage points. Notably, some schedules demonstrated a greater than 30 % standardized incidence (AZ-AZ-BNT and AZ-AZ-MOD), while others showed less than 20 % standardized incidence (MOD-MOD-BNT).

Previous studies have shown that heterologous vaccination is safe and effective, causing no greater side effects than homologous vaccination and producing a quantitatively superior antibody response compared to homologous vaccination [22].

The mixed vaccination approach could provide the immune system with a wider selection of humoral and cellular-mediated responses (B cells, T cells) to recognize the virus, as it could provide the immune system with slightly different conformation of SARS-CoV2 spike proteins [23].

Our study aimed to test these hypotheses with real world data by examining the incidence of SARS-CoV2 infection in the adult population of the province of Lecce, Apulia Region, after the booster dose.

Over 60 % of subjects included in the study received a homologous vaccination schedule, despite no scientific evidence supporting its superiority nor recommended by the Italian Ministry of Health. This imbalance could be due to the perceived safety of the homologous vaccination, having received a certain vaccine brand for the primary immunization cycle could have led to a preference toward the same vaccine for the booster dose in absence of scientific evidence supporting one strategy over the other [24].

One of the limitations of our study is that not having data on the unvaccinated individuals we are not able to calculate the vaccine effectiveness of the booster dose, however this outcome is beyond the objective of this study. The cumulative incidence of SARS-CoV2 infection after the booster dose in our study population is 26.61 %. The age-adjusted incidence varies among different schedules, ranging from 34.67 % to 18.93 %, with the highest in groups receiving two doses of AZ in the first immunization cycle (schedules 7 and 8). The findings on the worst performance of AZ product are confirmed as statistically significant by the common odds ratio confronting schedules 7 and 8 with homologous vaccination, showing the risk of infection doubling when comparing both AZ-AZ-BNT and AZ-AZ-MOD with schedule 2 (MOD-MOD-MOD).

Other potential limitations of the study, that should be considered in interpreting the results, are the absence of data on COVID19 severity and the not-controlled not-random choice of vaccination schedule by the subjects that could have led to some unknown bias in group assignment. Furthermore, the inclusion of both symptomatic and asymptomatic cases may have introduced some variability in the analysis, as the reasons for testing may differ among asymptomatic individuals. Although contact tracing was actively implemented throughout the study period to test and isolate each contact of a case, some asymptomatic individuals might not have been detected.

Moreover, we couldn't evaluate COVID19 vaccines specifically designed against the SARS-CoV2 Omicron variant since they were authorized by AIFA only in September 2022 [25].

We found that among the various schedules administered during the vaccination campaign, there were significant differences in terms of outcomes, not only when comparing viral vector and mRNA vaccines, but also when the booster used to recall a mRNA vaccine primary cycle. The only schedules that did not show a statistically significant difference were n° 11 and 12 (AZ-BNT-MOD and AZ-MOD-BNT), probably due to the small number of subjects.

The fact that all heterologous schedules, except the ones including AZ, showed a lower risk of infection compared with the homologous schedules highlights the superiority of COVID19 heterologous booster vaccination in preventing SARS-CoV2 infection. The real-world higher incidence of Omicron SARS-CoV2 infections following an AZ-AZ-mRNA vaccination schedule questions the effectiveness of neutralizing antibodies in preventing specifically Omicron infections as observed in vitro (in primary cycle heterologous AZ-BNT) [26].

The observed superiority of BNT-BNT-MOD over BNT-BNT-BNT and of MOD-MOD-BNT over MOD-MOD-MOD, as well as the better performance of JNJ-MOD in comparison of AZ-AZ-MOD and of JNJ-BNT in comparison of AZ-AZ-BNT, highlights a better performance of heterologous vaccination related to the vaccine product itself rather than the vaccine platform. This could be explained by the existence of an unknown immunological mechanism that should be investigated as it

could be useful to choose the best COVID19 vaccination schedule to tackle the Omicron variant of SARS-CoV2, as well as future variants of concern.

Comparing the effectiveness of different combinations in terms of infection prevention, our study lays the foundation for further questions. A good antibody response with heterologous vaccination, as shown by other studies [27,10], does not necessarily mean that combination is superior. Other factors must be involved in the superiority that the MOD-MOD-BNT schedule seems to have over MOD-MOD-MOD or BNT-BNT-MOD over BNT-BNT-BNT. The different amount of mRNA contained in the dose administered for the primary cycle and for the booster, the delivery system or self-adjuvanting properties could also play a role [28].

It is noteworthy that heterologous vaccination could represent a viable solution to vaccine availability challenges, particularly in low to middle-income countries. This approach introduces greater flexibility into the supply chain and, according to our data, offers comparable or even superior protection. The endorsement of heterologous vaccination by the World Health Organization (WHO) and the European Medical Agency (EMA) has been in place since 2021. This endorsement was based on emerging data indicating an increased level of protection against symptomatic disease when an mRNA vaccine was used as a boost during the period of the Delta variant's prevalence [29,30]. Our research provides critical data pertaining to the strategy of mix-and-match boosting, specifically during the time when the Omicron variant became the dominant strain within the study population. It is crucial to underscore that, as of 2023, the Omicron variant, inclusive of its various subvariants, maintains its prevalence a year later.

However, the public's apprehension towards this approach must be addressed through accurate and accessible information. This is especially crucial as novel vaccine formulations are being developed, presenting new opportunities for improved immunization strategies.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Luigi De Angelis, Francesco Baglivo, Mariano Magrì, Martina Minelli, Valerio Aprile, Raffaele Stifini and Pier Luigi Lopalco have no conflict of interest to declare. Caterina Rizzo participated in Advisory Board and Expert scientific discussion for Seqirus, MSD, GlaxoSmithKline (GSK), Sanofi and Astrazeneca. Alberto Fedele participated in Advisory Board and Expert scientific discussion for Seqirus.

Data availability

Data will be made available on request.

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Authors' contributions

Francesco Baglivo and Mariano Magrì conceived the paper. Francesco Baglivo, Martina Minelli and Luigi De Angelis performed the literature search and drafted the manuscript. Raffaele Stifini performed the data extraction and preprocessing. Caterina Rizzo, Alberto Fedele, Valerio Aprile and Pier Luigi Lopalco provided expert insights and contributed to the manuscript revision. All the authors approved the final manuscript.

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Ethics

The study was approved by the Ethical Committee "Comitato Etico Area 3 - ASL Lecce" of the Local Health Authority Lecce (ASL LE), Lecce, Italy (Prot. 0000212 29-05-2023).

Declaration of AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve readability, for English grammar check and to assist with translation from Italian to English of Sections 2.1 and 2.2. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.07.055.

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