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Relative vaccine effectiveness of the booster dose of COVID-19 vaccine for preventing death in individuals with a primary regimen based on the BBIBP-CorV, ChAdOx1-S, or BNT162b2 vaccines during the Omicron wave in Peru: A nested case-control study using national population data

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ABSTRACT

Background: Studies have reported evidence about the effectiveness of a third dose with BNT162b2 for preventing hospitalization and death by COVID-19. However, there is little evidence regarding other primary vaccine schedules such as BBIBP-CorV and ChAdOx1-S. We estimated the relative vaccine effectiveness (RVE) of the booster dose versus the primary regimens of COVID-19 vaccines based on BBIBP-CorV, ChAdOx1-S, or BNT162b2 for preventing death during the Omicron wave in Peruvian adult people.
Methods: We carried out a nested case-control study with a risk set sampling of controls using data from Peru between December 20, 2021, and February 20, 2022 (during the Omicron wave). Data on vaccination, COVID-19 tests and deaths were collected from national surveillance databases. We performed conditional logistic regression models to estimate the RVE on the adult population. In addition, we executed sub-group analysis per age group (18 to 59 years, and 60 years or more) and per primary regime (based on BNT162b2, BBIBP-CorV, or ChAdOx1-S).
Results: Of the 11,188,332 people eligible to enter the study 1,974 met the case definition (death from COVID-19) and were matched to 9,183 controls. The overall RVE of a third dose to prevent death was 87.2% (84.2%-89.7%), which varied according to the primary regime (87.3% for BNT162b2, 82.0% for BBIPB-CorV-2, and 79.5% for ChAdOx-S). In older adults, the RVE was 87.1%, without significant variations according to the primary regime (86.1% for BNT162b2, 86.1 for BBIBP-CorV, and 82% for ChAdOx-S).
Conclusions: The booster) dose of vaccine against COVID-19 had a high RVE for preventing death by COVID-19 in the Peruvian population in all primary regimes of vaccines during the Omicron wave. This effect was consistent in people over 60 years of age, the group most vulnerable to die from this infection.

1. Introduction

The COVID-19 pandemic harmed health systems, especially in low- and middle-income countries [1]. With an inequitable, fragmented, and segmented health system [2], Peru – a developing Latin American country - has been deeply affected, as evidenced by the highest mortality rate and excess mortality worldwide [3,4]. Amid the pandemic, vaccination against COVID-19 has proven to be a crucial public policy in controlling the pandemic disaster [5,6]. However, dealing with high demand and reduced supply worldwide, there have been variations in COVID-19 vaccination regimes and coverage between countries, especially in low-and middle-income countries [7,8].

Peru launched its National Vaccination Program against COVID-19 in February 2021 [9]. As in many Latin American countries, it began using inactivated vaccines from China [10]. Initially, the BBIBP-CorV vaccine (® Sinopharm) was used to vaccinate

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healthcare workers. Later, when mRNA vaccines became available for more countries, BNT162b2 (® Pfizer-BioNTech) was given to older adults, while BBIBP-CorV and ChAdOx1-S (® AstraZeneca) were reserved for the general population. In all cases, the baseline scheme was two doses of the same vaccine. However, during the second half of 2021, the emergence of the new viral variants and the waning of population immunity conferred by the two doses of the vaccine [11] motivated many countries to apply a third (“booster”) dose of the vaccine despite the limited evidence and controversy in the global recommendations at that time [12].

Although the administration of the third dose was initially controversial, over time real-world evidence demonstrated its relative immunological and clinical effectiveness. There is wide literature reporting that the neutralization effect of the third dose could be effective against the different variants of concern, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and more recently Omicron (B.1.1.529) [13–15]. Several effectiveness studies, such as that by the Center for Disease Control and Prevention (CDC) of the United States (US) have reported a relative effectiveness of 90 % in preventing hospitalization and death by Omicron with a third dose of mRNA in individuals over 50 years of age who have received two previous mRNA vaccines [16]. Another study in the US that compared the effectiveness of 3 doses versus 2 doses of mRNA vaccines between April 2021 and November 2021 (before the identification of the Omicron variant) found an effectiveness of 85 % to prevent documented infection and 82 % for preventing hospitalization [17]. However, the published evidence for other combinations of vaccines (for example: with a primary schedule in inactivated or viral vector vaccines) is very scarce.

Data on the effectiveness of the third dose is mainly limited to certain specific combinations of vaccines. Throughout the pandemic, the Peruvian National Institute of Health performed evaluations of vaccination schemes to prevent contagion, serious illness, and death in operational conditions to estimate their impact and guide decision-making [18–21]. However, the evaluation of the peculiar mixture of vaccines generated in Peru is relevant, since few countries have applied the combination of receiving an mRNA vaccine after an initial schedule of BBIBP-CorV. Moreover, most studies assessing these combinations focus primarily on immunogenicity and safety rather than effectiveness [22–24].

Therefore, using the data from the COVID-19 national vaccination registry of Peru our study aimed to estimate the relative vaccine effectiveness (RVE) of the booster (three-dose regimen) versus the primary regimen (two-dose) of COVID-19 vaccination to prevent death in Peru during its third wave of contagion driven by the Omicron SARS-COV-2 variant in Peruvian adult people with an initial regimen based on the BBIBP-Cor-V, ChAdOx1-S, or BNT162b2 vaccines.

2. Methods

2.1. Study design and population queries

We carried out a nested case-control study with a risk set sampling of controls to estimate the relative effectiveness of three doses of vaccine against COVID-19 compared to two doses to prevent death due to COVID-19 as the main outcome. Although the third dose was administrated since October 2021 in Peru, we restricted the analysis to December 20, 2021 – February 20, 2022, to provide estimates of effectiveness during the Omicron wave in Peru.

We performed analyses of the general adult population (18 years or more) and sub-groupanalysis by age (18 to 59 years, and 60 years or more) and by each primary regimen BNT16b2, BBIBP-Cor-V or ChAdOx1-S). The RVE e of the third dose was estimated in all people regardless of their primary vaccination regimen. Secondarily, we provided regimen-specific estimates of RVE according to the causal contrast shown in **Figure S1**.

2.2. Sources of data and study population

We used three national surveillance databases: (i) The Ministry of Health national COVID-19 vaccination registry [25], (ii) The Integrated COVID-19 Register of antigenic and molecular tests (SISCOVID - Spanish acronym) [26], and (iii) The National Death System (SINADEF - Spanish acronym) [27]. These databases were linked in a deterministic way using a unique identification number provided by the Ministry of Health (MOH).

The MOH national COVID-19 vaccination registry is an electronic database created in 2021 which registers the basic information of the subjects who receive a COVID-19 vaccine, including their age, gender, address, if they are health personnel, number of doses and type of vaccine received, and date of vaccination. The SISCOVID has data on people who have received some health care for COVID-19 including the results of diagnostic tests to assess the history of previous infection. Finally, the SINADEF provided information on the deceased, including variables such as date and cause of death.

We integrated data using deterministic linkage and constructed a source cohort made of all people over 18 years of age included in the national COVID-19 vaccination registry who were alive on December 20, 2021 and for whom recorded basic demographic data were available. To include only incident users, people who received the third dose before December 20 were excluded. Those not eligible for vaccination with a third dose during the study period (time<3 months from the second dose or dying before being eligible) were also excluded from the analysis to reduce the risk of selection bias according to World Health Organization (WHO) recommendations [28].

2.3. Nested case-control

Time zero was defined as December 20, 2021 for people eligible to receive the third dose since the beginning of the study and for those who were not, time zero was defined as the day they became eligible to receive it (at least three months after the second dose according to Peruvian regulations) [29]. To account for the time-dependent nature of the vaccination status, subjects receiving the third dose during the study period were included in the period without the third dose as well as a second period after having received the third dose. Thus, one person could contribute with two-person periods: the first period during their time with the second dose and the second period after having received the third dose. The observations were censored on February 20, 2022 (administrative censoring) or when the participant died, whichever was first.

An observation was defined as a case of death registered in the SINADEF as a death due to COVID-19 (the ICD-10 codes registered included one of the following: U071, U072, B342, B972, or include the terms “coronavirus”, “cov-2”, “cov2”, “covid”, “covid19”, “SARS” or other closely related). The controls were selected among the persons who were still at risk when a case (death due to COVID-19) occurred. For each case, we selected a random sample without the replacement of a maximum of five controls using an incidence density sampling scheme. Control was matched with cases by confounding variables or prognostic factors of mortality. Specifically, we used coarsened exact matching by age (five-year bins) and time since second vaccination dose (five-day bins) and exact matching by sex, address (province), type of first vaccine dose, type of second vaccine dose, being a health care worker and having a previously documented

infection, defined as a positive test at least 90 days before the event (**Table S1**). Individuals selected as controls could be reused as controls for other cases and also become cases if they developed the outcome later.

2.4. Statistical analysis

We used conditional logistic regression to estimate the odds ratio of death due to COVID-19 in individuals vaccinated with three doses compared to those vaccinated with only two doses (primary regimen). It is important to note that in the nested case-control design and risk set sampling of control participants, the *odds ratio (OR)* from conditional logistic regression directly estimates the *incidence rate ratio (IRR)* without distortion by competing risks (death by other causes) and the rare outcome assumption [30]. Consequently, we estimated the *relative vaccine effectiveness (RVE),* which was calculated as (1 – OR) × 100 % and its 95 % confidence intervals (95 % CI).

We performed additional nested case-control for four different subpopulations. The main analysis was performed in all adult individuals, matched by the aforementioned variables without distinction of their primary vaccination regimen for all adults (18 years or more), young/middle-aged adults (18 to 59 years) and older adults (60 years or more). We also executed analyses considering the type of vaccine administrated as primary regimen. In the second analysis, the RVE of the booster dose was calculated only in the subpopulation of individuals whose first two doses had been of BNT162b2. The third analysis was made considering only the subpopulation of individuals whose first two doses had been of BBIBP-CorV and, finally, the fourth analysis was developed only on the subpopulation of individuals whose first two doses had been of ChAdOx1-S. We used with RStudio 4.1.2. ® (Rstudio, Boston, MA, USA) for all analyses.

2.5. Ethical aspects

Our study was approved by the Research Ethics Committee of the Peruvian National Institute of Health (INS Peru), (RD-561–2021-OGITT/INS). Authorization to access the different databases was requested from the Ministry of Health after the protocol had been approved.

3. Results

3.1. Selection, matching process, and characteristics of the participants

We identified 23,457,517 adult persons (18 years or more) alive as of December 20, 2021 (start of the study) for whom information was available in the national immunization registry. Of these, 11,188,332 people were eligible to enter the study and the source cohort was formed. After matching, 2,112 persons met the case definition (death by COVID-19) and were matched to controls. Of the 9,183 matched controls randomly selected from the risk set, 9,107 were unique, 76 were selected more than once, and eight were subsequently taken as cases due to death by COVID-19.

Fig. 1 shows the flow chart for the nested case-control selection carried out in the general population regardless of their primary vaccination regimen. **Figures S2-S4** show the flowcharts for the selection of nested case-control to evaluate the booster RVE in the population with the primary regimens constituted by two doses of BNT162b2 mRNA, BBIBP-CorV and ChAdOx1-S, respectively.

The demographic characteristics of the source cohort can be found in **Tables S2-S3**. The baseline characteristics of people who died of COVID-19 (cases) and their matched controls are shown in Table 1. Similar proportions for all categorical variables and cumulative distributions of age and time since the second dose

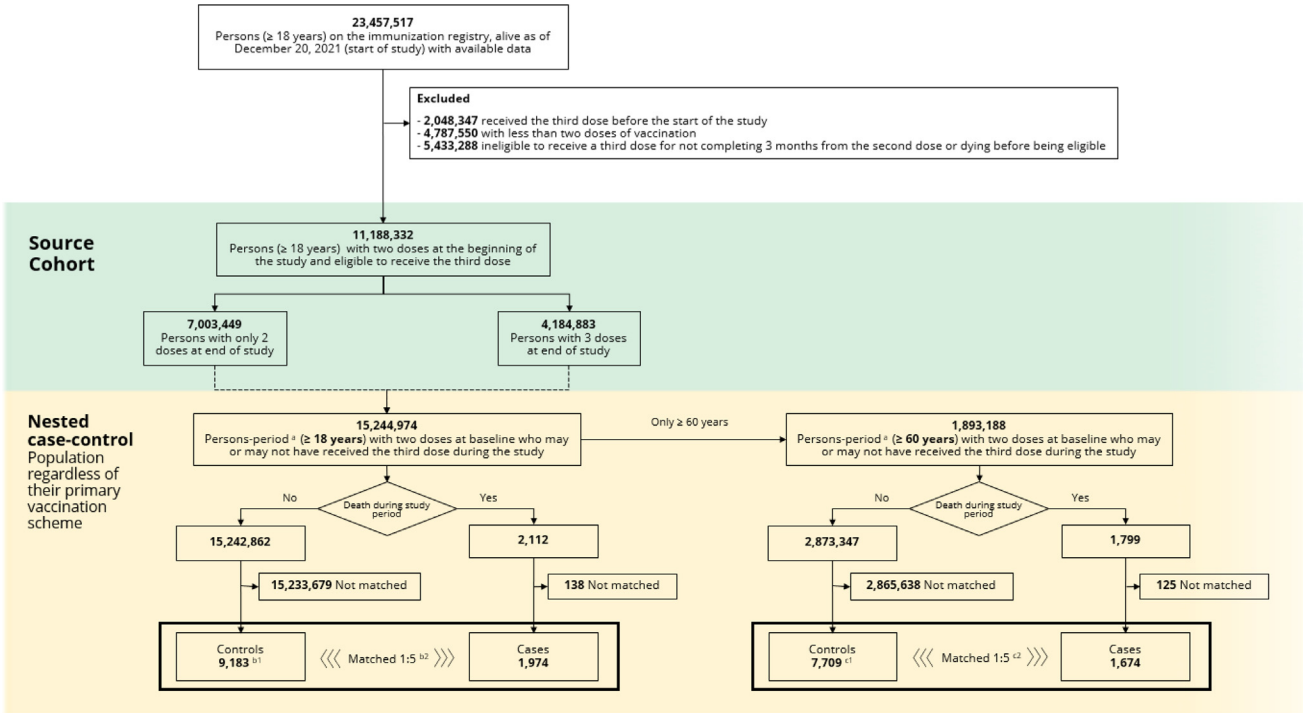

Fig. 1. Flowchart for the nested case-control selection carried out in the general population regardless of their primary vaccination scheme.. [a] Person-period: For nested case-control, a person could contribute with a period without a third dose and then re-enter the study and contribute with a second period with the third dose. [b1] 76 controls were sampled more than once, and 8 were subsequently taken as cases. [b2] 240 case-control sets were incomplete. [c1] 73 controls were sampled more than once, and 8 were subsequently taken as cases. [b2] 231 case-control sets were incomplete.

Table 1
Characteristics of the study population matched as cases and controls to evaluate the relative vaccine effectiveness of a booster (three doses schedule) of the COVID-19 vaccine during the Omicron wave in adult people. Perú 2021–2022.

	Nested Case-Control		
	Overall	Cases	Matched controls
Total	N = 11,157	N = 1,974	N = 9,183 [a]
Sex			
Female	4,641 (41.6 %)	818 (41.4 %)	3,823 (41.6 %)
Male	6,516 (58.4 %)	1,156 (58.6 %)	5,360 (58.4 %)
Age			
Median (Range)	77.0 (18.0–104.0)	78.0 (18.0–104.0)	77.0 (19.0–104.0)
Age group			
17 to 39	263 (2.4 %)	46 (2.3 %)	217 (2.4 %)
40 to 59	1,511 (13.5 %)	254 (12.9 %)	1,257 (13.7 %)
60 to 69	1,940 (17.4 %)	327 (16.6 %)	1,613 (17.6 %)
≥70 years old	7,443 (66.7 %)	1,347 (68.2 %)	6,096 (66.4 %)
Health care worker			
Yes	27 (0.2 %)	7 (0.4 %)	20 (0.2 %)
No	11,130 (99.8 %)	1,967 (99.6 %)	9,163 (99.8 %)
Previous infection			
Yes	676 (6.1 %)	124 (6.3 %)	552 (6.0 %)
No	10,481 (93.9 %)	1,850 (93.7 %)	8,631 (94 %)
Type of vaccine 1° dose			
ChAdOx1-S	1,069 (9.6 %)	197 (10.0 %)	872 (9.5 %)
BBIBP-CorV	1,045 (9.4 %)	198 (10.0 %)	847 (9.2 %)
BNT162b2	9,043 (81.1 %)	1,579 (80.0 %)	7,464 (81.3 %)
Type of vaccine 2° dose			
ChAdOx1-S	1,069 (9.6 %)	197 (10.0 %)	872 (9.5 %)
BBIBP-CorV	1,045 (9.4 %)	198 (10.0 %)	847 (9.2 %)
BNT162b2	9,043 (81.1 %)	1,579 (80.0 %)	7,464 (81.3 %)
Type of vaccine 3° dose			
Not recieved	6,931 (62.1 %)	1,762 (89.3 %)	5,169 (56.3 %)
ChAdOx1-S	38 (0.3 %)	0 (0.0 %)	38 (0.4 %)
BBIBP-CorV	—	—	—
BNT162b2	4,188 (37.5 %)	212 (10.7 %)	3,976 (43.3 %)
Time since 2° dose [b]			
Median (Range)	189.0 (90.0–268.0)	191.0 (90.0–268.0)	189.0 (90.0–266.0)

[a] 9,107 unique controls. Each case is matched up to 5 controls considering age, province of residence, type of vaccine in the 1st dose, type of vaccine in the 2nd dose, previous infection, the time elapsed since the 2nd dose, and being a health care worker.
[b] Time from 2nd dose to the start of the follow-up.

(**Figure S5**) demonstrate that balance between potential confounders was achieved.

3.2. Relative vaccine effectiveness of the booster dose of the COVID-19 vaccine

The estimated RVE to prevent death from COVID-19 of the booster COVID-19 vaccine compared to having received only the primary regimen (two doses) was 87.2 % (95 % CI: 84.2–89.7) in the adult population (Table 2). For persons previously vaccinated with two doses of BNT162b2 and the booster dose of BNT162b2, the RVE was 87 % (95 % CI: 84.1–89.8) compared to those who received only two doses. For persons who previously received two doses of BBIBP-CorV followed by a third dose of BNT162b2, the RVE for preventing death due to COVID-19 was 82 % (95 % CI: 58.2–92.2); while those who had previously received two doses of ChAdOx1-S showed a 79.5 % (95 % CI: 54.2–90.8) RVEafter receiving the booster dose of BNT162b2 compared to those who received only the primary regimen.

In young and middle-aged adults (18 to 59 years), the estimated RVE of the booster dose was 88.0 % (95 % CI: 79.1–93.1) (Table 3). In persons who previously received two doses of BNT162b2 followed by a third dose of BNT162b2, the RVE was 91.9 % (95 % CI: 83.4–96.1). Otherwise, for those who received two doses of

Table 2
Relative vaccine effectiveness of a third dose of the COVID-19 vaccine during the Omicron wave in adult people (18 years or older). Perú 2021–2022.

	Cases (Deaths)	Effectiveness of a third dose (95 % CI)	p-value
All adults regardless of the primary scheme			
Two doses	1,762/8,161 (21.6)	Ref.	
Three doses	212/2,996 (7.1)	87.2 (84.2–89,7)	p < 0.001
Adults with the primary scheme of BNT162b2			
Two doses (PFZ-PFZ-0)	1,398/6,314 (22.1)	Ref.	
Three doses (PFZ-PFZ-PFZ)	181/2,729 (6.6)	87.3 (84.1–89.8)	p < 0.001
Adults with the primary scheme of BBIBP-CorV			
Two doses (BIBP-BIBP-0)	180/881 (20.4)	Ref.	
Three doses (BIBP-BIBP-PFZ)	18/160 (11.3)	82.0 (58.2–92.2)	p < 0.001
Adults with the primary scheme of ChAdOx1			
Two doses (AZ-AZ-0)	184/920 (20.0)	Ref.	
Three doses (AZ-AZ-PFZ)	13/149 (8.7)	79.5 (54.2–90.8)	p < 0.001

PFZ: BNT162b2 Pfizer-BioNTech ®, BIBP: BBIBP-CorV Sinopharm ®, AZ:ChAdOx1-S Astrazeneca®.
Each case is matched up to 5 controls considering age, province of residence, type of vaccine in the 1st dose, type of vaccine in the 2nd dose, previous infection, the time elapsed since the 2nd dose, and being a healthcare worker.

Table 3
Relative vaccine effectiveness of the third dose of the vaccine to prevent COVID-19 deaths in young and middle-aged adults (18–59 years) during the Omicron wave in Peru, 2021–2022.

	Cases (Deaths)	Effectiveness of a third dose (95 % CI)	p-value
All young adults regardless of the primary scheme			
Two Doses	265/1312 (19.5)	Ref.	p < 0.001
Three Doses	35/453 (7.7)	88.0 (79.1 to 93.1)	
Young adults with the primary scheme with PFZ			
Two Doses (PFZ - PFZ)	156/720 (21.7)	Ref.	p < 0.001
Three Doses (PFZ - PFZ - PFZ)	24/346 (6.9)	91.9 (83.4 to 96.1)	
Young adults with the primary scheme with SNP			
Two Doses (SNP - SNP − 0)	102/566 (18.0)	Ref.	p = 0.02
Three Doses (SNP - SNP - PFZ)	11/100 (11.0)	66.6 (20.0 to 86.8)	
Young adults with the primary scheme with AZ			
Two Doses (AZ - AZ − 0)	7/24 (29.2)	Ref.	
Three Doses (AZ - AZ - PFZ)	0/4 (0.0)	NE	

PFZ: BNT162b2 Pfizer-BioNTech ®, BIBP: BBIBP-CorV Sinopharm ®, AZ: ChAdOx1-S Astrazeneca®, NE: Not estimable.
Each case is matched up to 5 controls considering age, province of residence, type of vaccine in the 1st dose, type of vaccine in the 2nd dose, previous infection, the time elapsed since the 2nd dose, and being a healthcare worker.

Table 4
Relative vaccine effectiveness of a third dose of the COVID-19 vaccine during the Omicron wave in elderly adults (60 years or older). Perú 2021–2022.

	Cases (Deaths)	Effectiveness of a third dose (95 % CI)	p-value
All older adults regardless of the primary scheme			
Two doses	1,497/6,786 (22.1)	Ref.	
Three doses	177/2,597 (6.8)	87.1 (83.9–89.7)	p < 0.001
Older adults with the primary scheme of BNT162b2			
Two doses (PFZ-PFZ-0)	1,242/5,651 (22.0)	Ref.	
Three doses (PFZ-PFZ-PFZ)	157/2,326 (6.7)	86.1 (82.5–89.0)	p < 0.001
Older adults with the primary scheme of BBIBP-CorV			
Two doses (BIBP-BIBP-0)	78/326 (23,9)	Ref.	
Three doses (BIBP-BIBP-PFZ)	7/49 (14.3)	86.1 (38,7–96,9)	p = 0.009
Older adults with the primary scheme of ChAdOx1			
Two doses (AZ-AZ-0)	177/617 (28.7)	Ref.	
Three doses (AZ-AZ-PFZ)	13/103 (12.6)	82.1 (57,3–92,5)	p < 0.001

PFZ: BNT162b2 Pfizer-BioNTech®, BIBP: BBIBP-CorV Sinopharm®, AZ: ChAdOx1-S AstraZeneca®.
Each case is matched up to 5 controls considering age, province of residence, type of vaccine in the 1st dose, type of vaccine in the 2nd dose, previous infection, the time elapsed since the 2nd dose, and being a health care worker.

BBIBP-CorV followed by a third dose of BNT162b2 the RVE was 66.6 % (95 % CI: 20.0–86.8). The RVE of those who received two doses of BBIBP-CorV followed by a third dose of ChAdOx1-S could not be estimated since there were no events (deaths) in this specific population.

In the elderly population (60 years or more), the estimated RVE was 87.1 % (95 % CI: 83.9–89.7) (Table 4). Likewise, in older adults who had received BNT162b2 or BBIBP-CorV as the first two doses, the RVE of a third dose of BNT162b2 to prevent death was 86.1 %. However, we must point out that the CI was lower in persons previously vaccinated with BBIBP-CorV (95 % CI: 38.7–96.9) than in those previously vaccinated with BNT162b2 (95 % CI: 82.5–89.0). Finally, in older adults who had received the first two doses with ChAdOx1-S, a third dose of BNT162b2 had a RVE of 82.1 % (95 % CI: 57.3–92.5).

We present the estimations and their 95 % CIs graphically for both age-subgroups in Fig. 2.

4. Discussion

4.1. Main findings

In our real-world study, the relative vaccine effectiveness of the booster (three-dose regimen) of the COVID-19 vaccine was 87.2 % to prevent death due to COVID-19 in the Peruvian adult population, during the third wave of contagion driven by the Omicron variant in comparison to having received only the primary regimen (two-doses) of the COVID-19 vaccine. This finding could be interpreted as a reduction of nearly 90 % of deaths in the group with three doses.

The estimated RVE was similar across all the primary regimes administrated. In people who received primary vaccination with BNT162b2, the effectiveness was 87 %, 82 % in those who received primary vaccination with two doses of BBIPB-CorV-2 and 79.5 % in those receiving ChAdOx-S. Overall, regardless of the primary vaccine received, the three sregimes showed high effectiveness in preventing death due to COVID-19. Our study was not intended to compare the RVE of these regimes; however their 95 % confidence intervals overlap, indirectly indicating no significant differences between them.

The relative vaccine effectiveness was 87.1 % in the elderly, without large variations according to the primary scheme (86.1 % for BNT162b2, 86.1 for BBIBP-CorV, and 82 % for ChAdOx-S). These consistent results in the elderly population are important, as the effectiveness of vaccines against COVID-19 can be lower as age increases, due to immunosenescence and comorbidities, among other factors. In addition, the RVE in young/middle-aged people

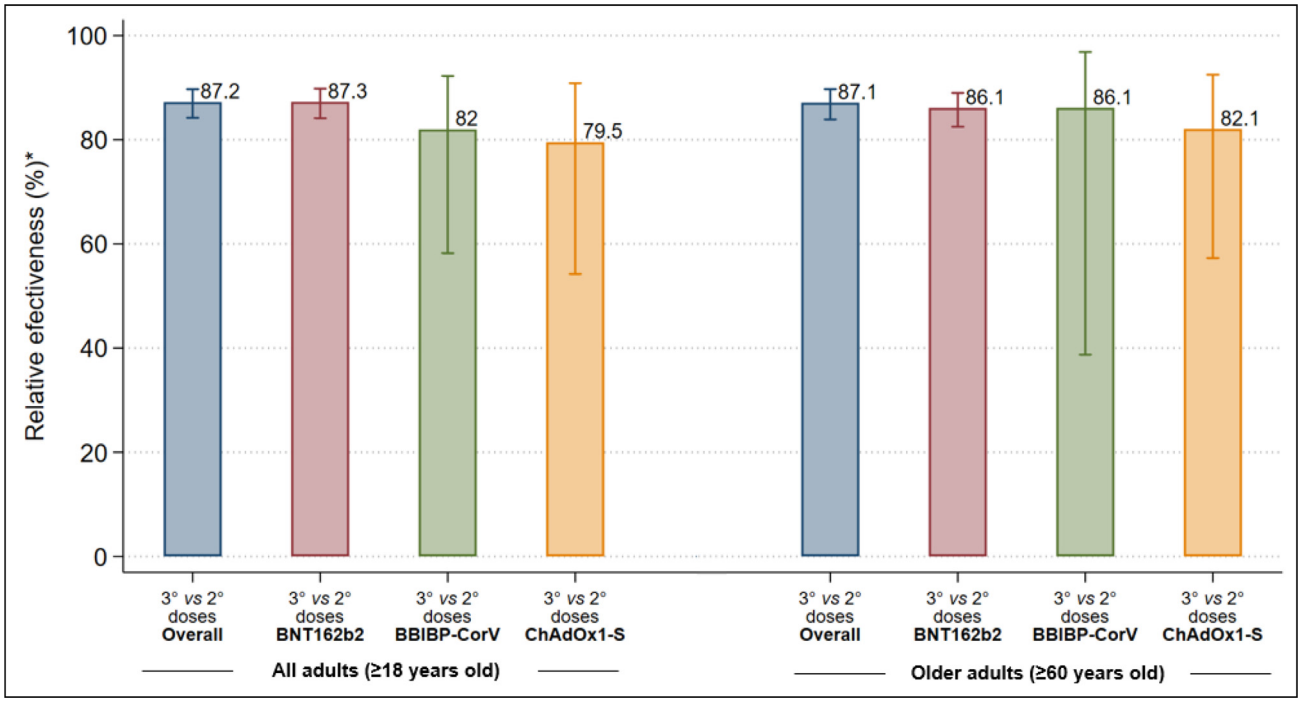

Fig. 2. Relative vaccine effectiveness of the third dose to prevent death from COVID-19 during the Omicron wave in Peru. Analysis in the general population and according to the type of vaccine received in the first two doses. Note. (1-OR) x100: Nested case-control models paired by age, province of residence, type of vaccine in the 1st dose, type of vaccine in the 2nd dose, previous infection, the time elapsed since the 2nd dose, and being a health care worker. BNT162b2: Pfizer-BioNTech®, BBIBP-CorV: Sinopharm®, ChAdOx1-S: Astrazeneca®.

(18 to 59 years) was similar (88.0 %), although, in the analysis for each type of booster vaccine, we observed differences regarding the precision of the estimations.

4.2. Comparison with previous literature

Our figure is concordant with previous studies evaluating the booster dose, such as the study carried out by the CDC in the US, in which the booster (third) dose received during the Omicron wave was 82 % effective in preventing emergency care and 90 % in preventing hospitalization associated with COVID-19 [31]. Other reports include the 21 studies on vaccine effectiveness during the Omicron wave described in the last report from a meeting of the WHO published in April 2022, in which it was found that the third dose of vaccine was 75 % effective in preventing outcomes such as serious illness and hospitalization in almost all cases within the first and third month. [32] We have not found a published evaluation of the effectiveness of the third dose in a population that has received BBIBP-CorV (Sinopharm ®) as one of their primary regimens. Another study with an inactivated virus vaccine (CoronaVac ®) as the primary regimen reported relative vaccine effectiveness of 71.3 % in the prevention of severe disease with the homologous regimen (if the third dose was also of the same type) and 85.5 % with the heterologous regimen (if the third dose was different to Coronavac ®) [33].

4.3. Plausibility and explanation of the results

The almost uniform effectiveness of the three vaccine schedules may have several explanations. First, there is vast literature available on the advantages of the mixed vaccines strategy. Having various kinds of epitopes triggers different kinds of antibodies and cells, thereby providing a more comprehensive immune response than using the same antigen, as in the scheme of three doses of BNT162b2 [23,34]. Additionally, our evaluation was performed during the Omicron wave, a variant of concern in which has been hypothesized to have a high ability of "immune evasion", as evidenced by the significantly lower neutralization of this variant by the sera of vaccinated individuals compared to all the other viral variants [31,35] by all vaccines. If the effectiveness of all the vaccines is so significantly diminished by this immune evasion, this could help to homogenize the estimates for all the regimes. Moreover, our study was not designed to find differences between the specific vaccine schedules against COVID-19, and thus, any differences between them would have gone unnoticed.

4.4. Limitation and strengths

Our analysis has some limitations that should be recognized. First, there are drawbacks to using data from national information systems designed for another main purpose. For example, the data from the vaccination registry was never intended to be used to answer research questions, but rather its purpose was to monitor vaccination compliance in the Peruvian population. Thus, data may have been collected less strictly and some records may have invalid or missing self-reported data. Second, it was only possible to match with the available variables. This means that, unlike a randomized controlled trial, it is not possible to balance other unknown and unmeasured characteristics of the population. However, we were able to work with important matching factors, including age, type of previous vaccination, location (province level), and time since the second dose, to avoid most confounders. Although we could not match for comorbidities due to the quality of the records, we performed a supplementary analysis with comorbidities and the overall results were maintained (see **Table S4**). Third, we were not able to evaluate the relative effectiveness against infection and hospitalization because the national registries do not allow this. In the case of a history of infection, although we matched for this variable, it only included those officially registered; for example, until November 2021, only 7.2 to

14.0 % of infections by SARS-COV2 were registered in Peru [36]. Fourth, in a methodology that allows people to be selected as controls several times, it is possible to duplicate a specific subset of participants that could disproportionately influence the results. In our case, due to the large population in the source cohort (11,188,332 people) and the fact that only 76 persons were sampled as controls more than once, we consider that this duplication had a minimal impact on our estimations. Fifth, a small number of the adult population received the BBIBP-CorV vaccine as a booster (n = 179), this is related to the policies dictated by the government as part of the vaccination program. Likewise, only about 1.2 % of the population received ChAdOx1-S as a booster and there were no events (deaths) recorded in this subpopulation. However, the objective of our study was focused on estimating the relative vaccine effectiveness of the booster (three doses schedule) regardless the COVID19 vaccine used. Although, with an exploratory approach, we perform RVE calculations according to the primary schemes and the booster administrated.

Despite these limitations, we consider that our study has several strengths, such as the use of nationwide registers to provide population estimates of the effectiveness of the COVID-19 vaccines in a period during which Omicron was the most predominant variant. Also, performing a nested case-control study is considered an adequate approach for the assessment of vaccine effectiveness, this approach has been recognized by the WHO as one of the most useful designs for this objective [28]; in particular, the calculated OR from a conditional logistic regression allows us to estimate directly the incidence rate ratio [30].

4.5. Implications for public health and policy

The high relative effectiveness is relevant because, despite the peculiar characteristics of the Peruvian population, these estimates are consistent. Peru showed a very high rate of previous natural infection due to SARS-CoV-2 [36] and a very high rate of reinfections compared to other countries [37,38]. This might lead to the assumption that the third dose of vaccine could have been less effective than in other countries due to our more-intensely built natural population immunity. However, this was not the case and the estimate of relative effectiveness obtained was similar to that described in other countries with lower rates of previous infections [39,40].

The "similar" relative effectiveness between the different combinations is also an interesting finding, as mRNA vaccines are, in general, more effective than the other types of vaccines for preventing both infection and death [24,41]. However, in our study, the mix and match of both an inactivated virus vaccine with a third dose of an mRNA vaccine, and a viral vector vaccine with a third dose of an mRNA vaccine, showed equivalent effectiveness for the prevention of death due to COVID-19 with three doses of an mRNA vaccine.

The results regarding elderly people are an important message for health communication strategies since up to 69.8 % of deaths from COVID-19 were of people over 60 years of age in Peru [42,43] and similar to what happens in other low and middle-income countries, even now the coverage of the third dose is not adequate. The percentage of the population with three doses in Peru at the end of the Omicron wave (February 20, 2022) was only 40 % in the general population and 65 % in the older adult population. This situation has been especially critical in some regions such as Madre de Dios (Jungle) and Puno (Andean highlands) where the general coverage was still<20 % [44].

5. Conclusions

Globally, our findings demonstrate the high relative vaccine effectiveness of the booster dose of the COVID-19 vaccine to prevent death by COVID-19 in the Peruvian adult population. The effectiveness is consistent in elderly people, the group most vulnerable to die from this infection. The primary vaccination regimen received did not significantly affect the estimates, highlighting the decision of many Latin American governments to use several types of vaccines in parallel to ensure the coverage of their population when the mRNA vaccines were scarce. Every effort should be made to scale up the third dose in those who have not received it yet prioritizing the higher ranges of age.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.09.066.

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