


Účinnost vakcín mRNA-1273, BNT162b2 a BBIBP-CorV proti infekci a úmrtnosti u dětí v Argentině, během převahy delta a omikronových variant covid-19: test negativní, případová kontrolní studie

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Abstraktní

Cíl Odhadnout účinnost dvoudávkového očkovacího schématu (mRNA-1273, BNT162b2 a BBIBP-CorV) proti infekci SARS-CoV-2 a úmrtí souvisejícím s covid-19 a krátkodobému oslabení imunity u dětí (3-11 let)) a adolescenty (12-17 let) během období převahy delta a omikronové varianty v Argentině.

Design Test negativní, případová-kontrolní studie.

Nastavení databáze národního dozorového systému a nominovaného federálního očkovacího registru Argentiny.

Účastníci 844 460 dětí a dospívajících bez předchozí infekce SARS-CoV-2 způsobilých k získání základního očkovacího plánu, kteří byli testováni na SARS-CoV-2 polymerázovou řetězovou reakcí nebo rychlým antigenovým testem od září 2021 do dubna 2022. Po porovnání s odpovídajícím kontrol, 139 321 (60,3 %) z 231 181 případů zůstalo k analýze.

Expozice Dvoudávkové očkovací schéma mRNA-1273, BNT162b2 a BBIBP-CorV.

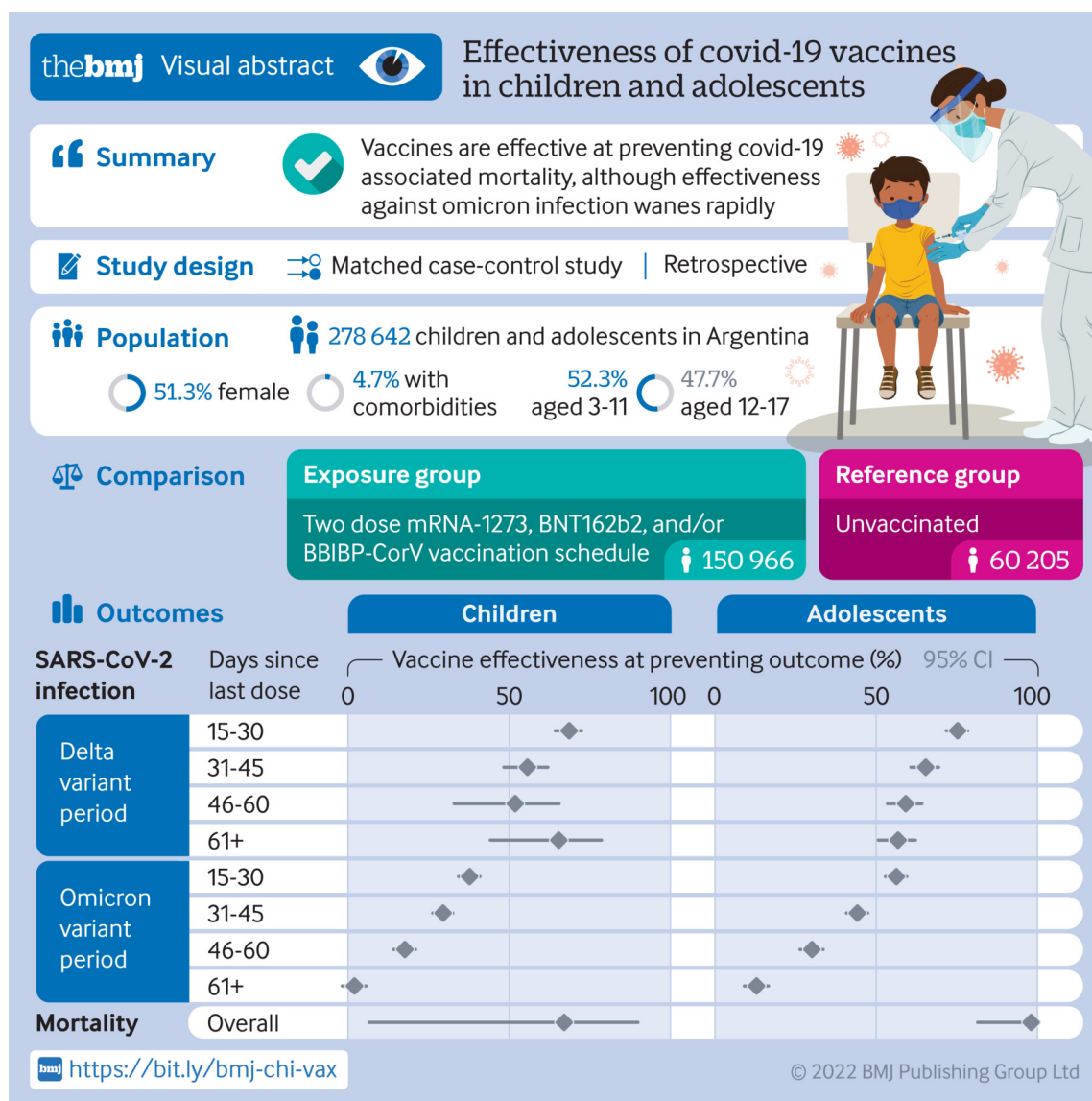
Hlavní výsledek měří infekci SARS-CoV-2 a úmrtí související s covid-19. K odhadu pravděpodobnosti infekce SARS-CoV-2 mezi dvěma dávkami očkovanými a neočkovanými účastníky byla použita podmíněná logistická regrese. Účinnost vakcíny byla odhadnuta jako $(1 - \text{poměr pravděpodobnosti}) \times 100 \%$.

Výsledky Odhadovaná účinnost vakcíny proti infekci SARS-CoV-2 byla 61,2 % (95% interval spolehlivosti 56,4 % až 65,5 %) u dětí a 66,8 % (63,9 % až 69,5 %) u dospívajících během delta dominantního období a 15,9 % (13,2 % na 18,6 %) a 26,0 % (23,2 % na 28,8 %), když byl dominantní omikron. Účinnost vakcíny v průběhu času klesala, zejména během omikronového období, z 37,6 % (34,2 % až 40,8 %) za 15–30 dní po očkování na 2,0 % (1,8 % až 5,6 %) po ≥ 60 dnech u dětí a z 55,8 % (52,4 % až 59,0 %) až 12,4 % (8,6 % až 16,1 %) u adolescentů.

Účinnost vakcíny proti úmrtí souvisejícím s infekcí SARS-CoV-2 během omikronové převahy byla 66,9 % (6,4 % až 89,8 %) u dětí a 97,6 % (81,0 % až 99,7 %) u dospívajících.

Závěry Účinnost vakcíny v prevenci úmrtnosti zůstala vysoká u dětí a dospívajících bez ohledu na cirkulující variantu. Účinnost vakcíny v prevenci infekce SARS-CoV-2 byla krátkodobě po očkování nižší během omikronové převahy a v průběhu času prudce klesala.

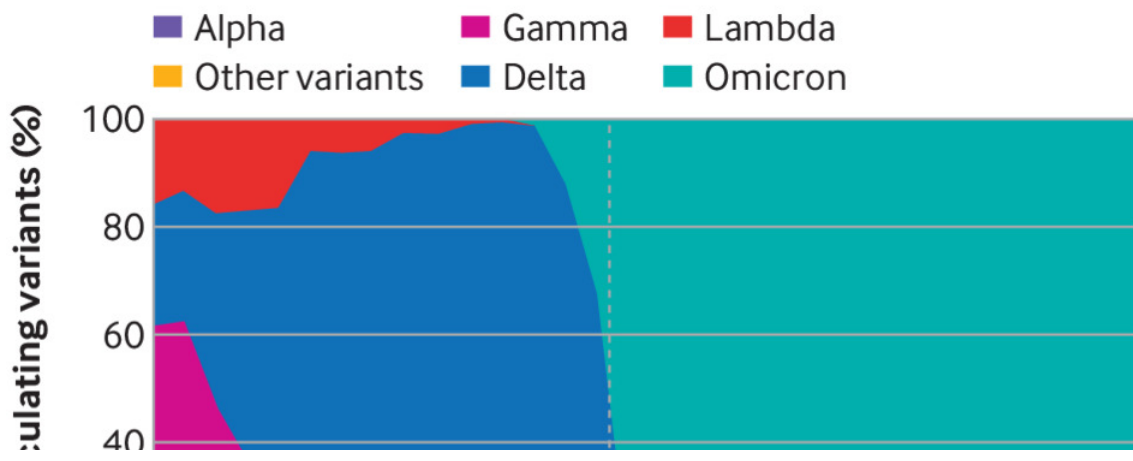
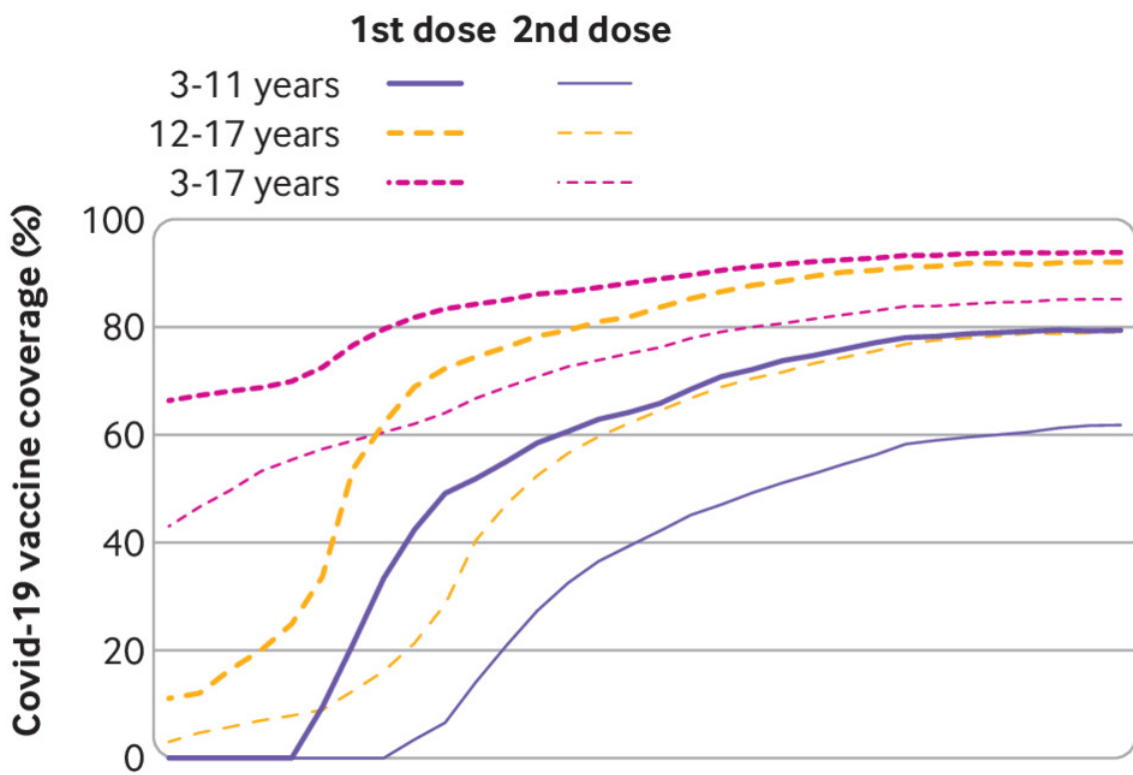
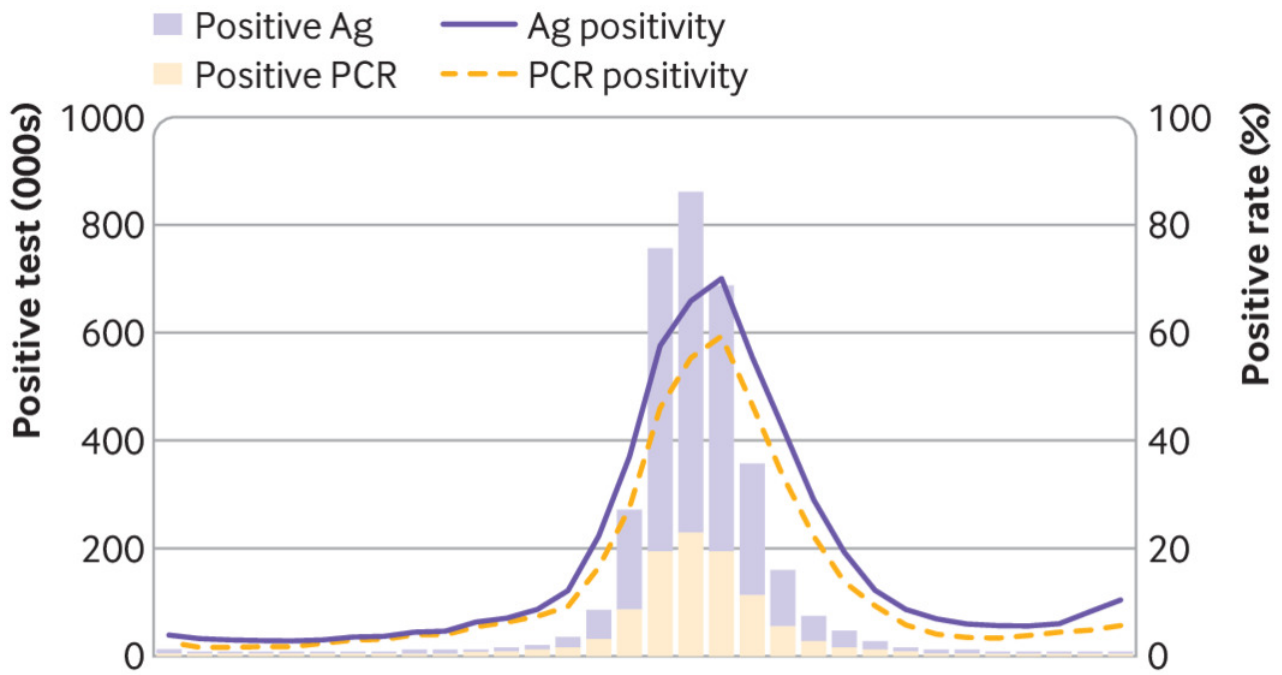
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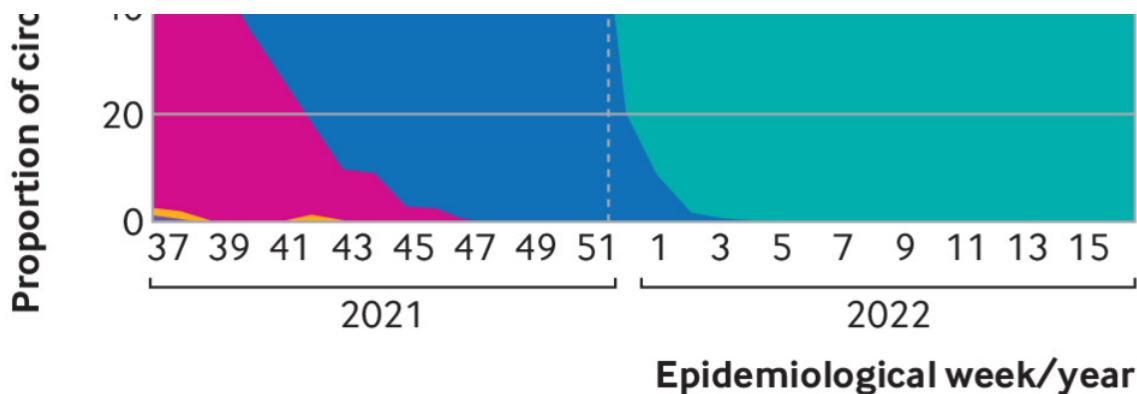


Úvod

Celosvětová očkovací strategie proti covid-19 změnila vývoj pandemie. Pozoruhodné bylo snížení nemocnosti a mortality u dospělých, kteří byli první prioritní populací vzhledem k jejich vysoké úmrtnosti. Na rozdíl od této populace je infekce v dětství a dospívání obvykle mírná, i když byly hlášeny i závažné případy s následky (například multisystémový zánětlivý syndrom) a dokonce s fatálními následky, zejména u pacientů s komorbiditami. ¹ V Argentině byla dětská populace testována molekulárními metodami (například reverzní transkripční polymerázovou řetězovou reakcí (RT-PCR)) a imunochromatografickými testy (například rychlým

antigenovým testem) (obr. 1, nahoře) a představovalo asi 8 % z celkového počtu potvrzených případů s úmrtností 0,05 %. 2 Srovnání účinnosti podle diagnostické metody pro tuto populaci nejsou k dispozici.





Obr. 1

Horní panel: případy incidentů a míra positivity na covid-19 podle roku, epidemiologického týdne a typu testu. Střední panel: proočkovanost podle roku a epidemiologického týdne podle věkové skupiny a aplikované dávky. Spodní panel: rozložení cirkulujících variant SARS-CoV-2 podle roku a epidemiologického týdne. Týdny 37-52 2021 a 1-16 2022. Ag=antigen; PCR = polymerázová řetězová reakce. Svislá tečkovaná čára označuje změnu převahy variant z delta na omikron

Bez ohledu na to, že očkování v této věkové skupině vyvolalo četné diskuse, bylo doporučeno mezinárodními vědeckými společnostmi, jako je Americká akademie pediatriů v květnu 2021 a argentinská Národní technická poradní skupina pro imunizaci (NITAG). 3,4 V roce 2022 navíc Světová zdravotnická organizace stanovila, že navzdory skutečnosti, že nejde o prioritní skupinu, 5 by mělo být dosaženo pokroku u pediatrické populace v zemích s vysokou proočkovaností dospělých. Očkování by mělo směřovat nejen k individuálnímu, ale i kolektivnímu prospěchu, protože by sloužilo ke zvýšení celkové imunity populace a ke snížení globálního přenosu.

V Argentině měla strategie očkování proti covid-19 za cíl postupně a progresivně očkovat 100 % prioritní populace. Priorita byla stanovena podle rizika závažnosti onemocnění, rizika expozice a sociální zranitelnosti. Na základě doporučení NITAG bylo v druhé polovině roku 2021 zahájeno očkování dospívajících ve věku 12 až 17 let, a to vakcínami mRNA-1273 (Spikevax, Moderna) a BNT162b2

(Comirnaty, Pfizer-BioNTech), po nichž následovaly děti ve věku od 3 do 11 let, kteří byli očkováni BBIBP-CorV (Sinopharm) (obr. 1 , uprostřed). 6 7 8 9

Ačkoli systematický přehled zjistil, že země s nízkým středním příjmem mohou mít větší podíl dětských úmrtí v důsledku covid-19 než země s vysokými příjmy, 10 důkazů o účinnosti očkování, zejména při prevenci úmrtnosti u dětí a dospívajících, je vzácné. 11 12 13 14. Některé studie hodnotily účinnost vakcíny pro inaktivované vakcíny, ale pouze jedna zahrnovala BBIBP-CorV a pouze dvě uváděly účinnost v prevenci infekce u dětí mladších 5 let. 15 16 17 18 Studie, která hodnotila účinnost vakcíny BBIBP-CorV u dětí, byla provedena v provincii Buenos Aires (Argentina) a odhadla, že účinnost vakcíny v prevenci hospitalizace u dětí ve věku 3–11 let byla 76,4 % (95% interval spolehlivosti 62,9 % až 84,5 %). Tato studie však nehodnotila účinnost pro prevenci infekce nebo úmrtnosti nebo ztráty účinnosti v průběhu času. 17

Kromě toho, ačkoli několik studií uvádělo v průběhu času pokles účinnosti vakcíny BNT162b2 u dětí nebo dospívajících, existuje jen málo důkazů o změnách účinnosti u inaktivovaných vakcín nebo o rozdílech souvisejících s variantami SARS-CoV-2. Kromě toho, navzdory skutečnosti, že studie o účinnosti vakcín covid-19 obvykle zahrnují případy diagnostikované jak pomocí RT-PCR, tak pomocí rychlých antigenních testů, nejsou k dispozici srovnání účinnosti podle diagnostické metody pro dětskou populaci.

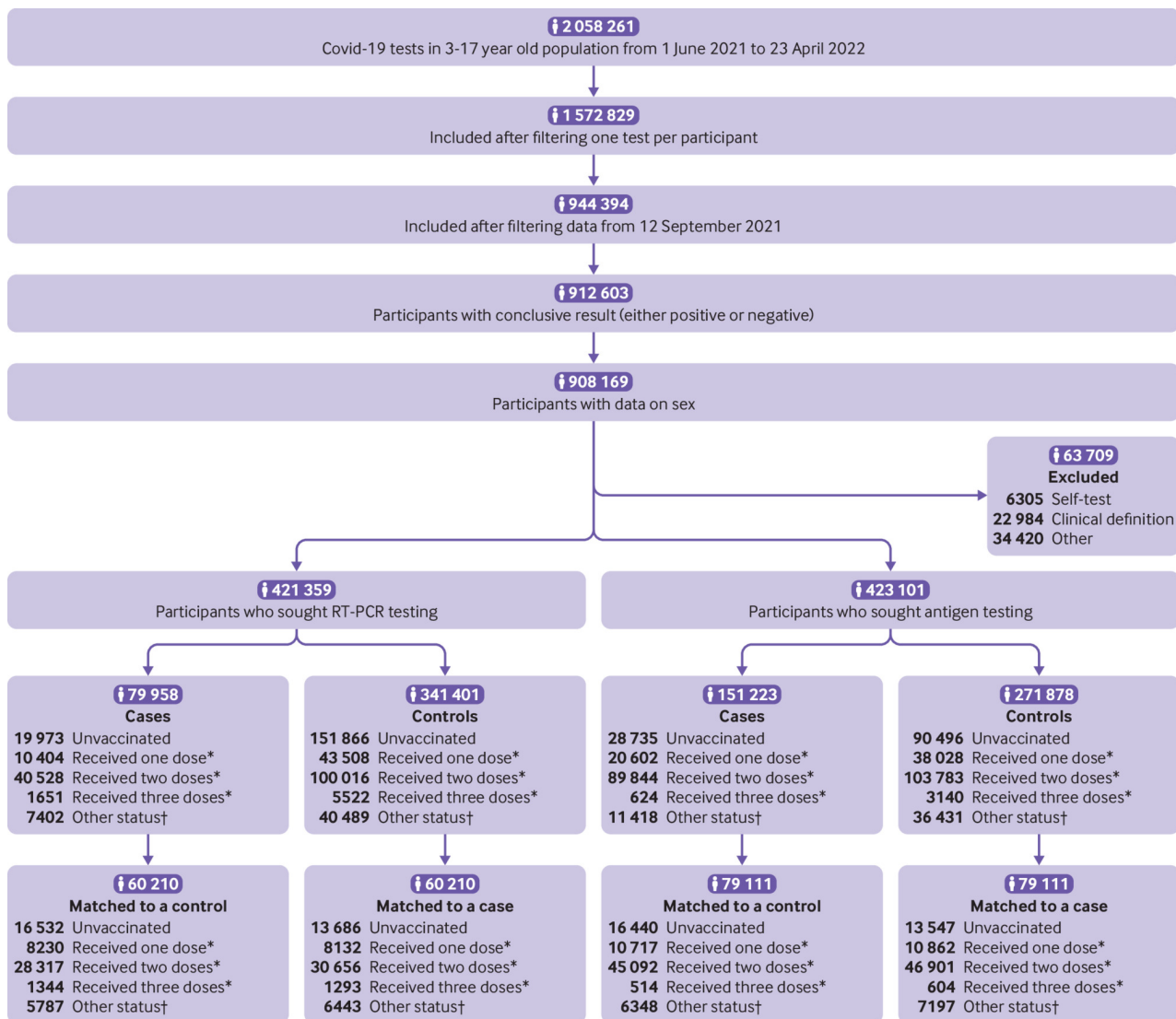
Proto bylo cílem této studie vyhodnotit účinnost dvou dávkovacích schémat vakcín mRNA-1273, BNT162b2 a BBIBP-CorV v prevenci infekce SARS-CoV-2 a úmrtí souvisejících s covid-19 u dětí a dospívajících ve věku 3 let. -17 let, během období převahy delty a omikronu BA.1 mezi zářím 2021 a dubnem 2022 v Argentině. Dále jsme se zaměřili na posouzení efektu diagnostické metody používané pro odhad účinnosti vakcíny, účinnosti různých kombinací mRNA vakcín a krátkodobého poklesu imunity u dětí a dospívajících.

Metody

Studujte populaci, prostředí a design

Tato studie se řídila negativním testem, případ-kontrola. Tyto návrhy se pokoušejí zajistit kontrolu nad zmatky v důsledku rozdílného zjišťování případů, přístupu k péči a chování při hledání zdraví. Jsou považovány za dostatečně silné, aby odhadly účinnost vakcín a byly široce používány pro tento účel u SARS-CoV-2, chřipky a dalších virů. [19](#) [20](#)

Argentina zahájila očkování dospívajících (ve věku 12–17 let) v srpnu 2021 a malých dětí (ve věku 3–11 let) v říjnu 2021. Všichni účastníci ve věku 3 až 17 let, kteří byli testováni na SARS-CoV-2 mezi 12. zářím 2021 a 23. dubna 2022 (s ohledem na období delta převahy do 25. prosince 2021 a období převahy omikronů od té doby) ([obr. 1](#), dole), bez předchozího pozitivního testu od 1. června 2021, byly způsobilé pro zařazení ([obr. 2](#)). Analýzy jsme omezili na účastníky, kteří vyhledávali RT-PCR nebo testování antigenu ve zdravotnických zařízeních nebo testovacích centrech. Do studie jsme zahrnuli účastníky pouze jednou, ať už jako případ nebo jako kontrolu. První pozitivní test ve sledovaném období byl považován za zařazení jako případ do primární analýzy, bez ohledu na počet předchozích negativních testů. Kontrolní byli ti účastníci, kteří byli v období studie testováni pouze negativně a byli vybráni v den svého prvního testu. Abychom vyhodnotili účinnost vakcíny proti úmrtnosti spojené s covid-19, zahrnuli jsme jako případy pouze ty účastníky, kteří byli pozitivně testováni v krátké době před smrtí. Národní epidemiologické oddělení navíc vyhodnotilo každý případ s příslušným odborem epidemiologie, aby potvrdilo příčinu smrti.



Obr. 2

Vývojový diagram studované populace. RT-PCR = polymerázová řetězová reakce s reverzní transkripcí. *Minimálně 14 dní mezi poslední dávkou a testem. †Mezi 1 a 14 dny od jakékoli dávky do testování; nekonzistence dat

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Zdroje dat a definice

Studie používala data epidemiologického dozoru z Národního systému dozoru (SNVS 2.0), přičemž byla zachována důvěrnost účastníků podle Helsinské deklarace a místních předpisů. Hlášení podezření na covid-19 a jejich potvrzení a výsledky prováděli

certifikovaní uživatelé (odborníci, technici, správní a zdravotnické úřady 24 okresů) z podsektorů veřejné zdravotnictví, soukromé zdravotnictví a sociální zabezpečení. Pro matriku úmrtí každý okres systematicky kontroloval a ověřoval údaje z jiných záznamů o úmrtích, jako jsou úřady životně důležitých záznamů (údaje z úmrtních listů), nemocnice a pohřební společnosti. Tato data byla začleněna do SNVS 2.0. Informace o vakcínách byly hlášeny v Nominalizovaném federálním registru očkování (NOMIVAC), včetně data očkování všech očkovaných účastníků, počtu dávek, typu vakcíny a očkovacího centra. Postupovali jsme podle kontrolního seznamu STROBE.²¹

Děti ve věku 3–11 let jsme považovali za plně očkované, pokud dostaly dvě dávky BBIBP-CorV a druhou dávku dostaly minimálně 14 dní před testováním. Dospívající ve věku 12–17 let jsme považovali za plně očkované, pokud dostali dvě dávky homologního nebo heterologního schématu s BNT162b2 a/nebo mRNA-1273 a druhou dávku dostali minimálně 14 dní před testováním. Jedinci, kteří nesplňovali tato kritéria, byli zahrnuti do analýz v tomto článku ve třech dalších kategoriích: ti, kteří dostali pouze jednu dávku minimálně 14 dní před testováním (částečně očkovaní), ti, kteří dostali tři dávky se stejným minimálním intervalem, a další. Třetí kategorie zahrnuje ty, kteří byli očkováni dva týdny před testem, ti, kteří dostali jinou vakcínu, a osoby s nekonzistentními nebo neúplnými údaji o očkování. Informace o variantách nebylo možné zjistit na individuální úrovni a při analýze našich výsledků jsme použili převládající variantu z dat ze sledování.

Výsledky

Primárním výsledkem této studie byla infekce SARS-CoV-2 potvrzená testováním antigenu nebo RT-PCR. Sekundárním výsledkem bylo úmrtí související s infekcí SARS-CoV-2.

Statistické analýzy

We matched cases and controls one to one on province of residence, week of testing, type of test (antigen or genomic), presence of comorbidities, sex, and age (± 1 year). Ties during matching were automatically and randomly resolved by the algorithm. Matching improves statistical efficiency in case-control studies and yields unbiased estimates when a model accounting for matching, such as conditional logistic regression, is used. The effect of the matching factors on the outcome cannot be estimated in matched sets and thus is a considerable disadvantage of matching. To compare characteristics between cases and test negative controls, we did descriptive analyses for the unmatched and matched cohorts. P values shown refer to Student's *t* test, Mann-Whitney U test, or Kruskal-Wallis rank sum test for differences in numerical variables or χ^2 tests for proportions.

We used conditional logistic regression to compare the odds of SARS-CoV-2 infection as a function of vaccination status, taking the matching pairs into consideration. We estimated vaccine effectiveness as $(1 - \text{odds ratio}) \times 100\%$ and presented it with its corresponding 95% confidence interval by using the profile likelihood method. We estimated the same intervals by using bootstrapping as a robustness analysis. We created 1000 resampled datasets of matched case-control pairs. The total number of participants in each sample was equal to that of the original dataset (or the subset, for subgroup analysis), but differences within datasets were due to allowing replacement when sampling. For each of these datasets, we fitted a conditional logistic regression model and calculated vaccine effectiveness as in the main analysis. We calculated bootstrapping based vaccine effectiveness by taking the mean of the 1000 resampled datasets and defined its confidence interval limits as the empirical centiles 0.25 and 97.5.

We classified vaccination status in different levels depending on the subanalysis. The unvaccinated group was the selected reference group in all the analyses. Other levels of the vaccination status

variable refer to participants who were partially vaccinated (at least 14 days between first dose and test), those who received three doses, and others (details in Data sources and definitions). The level of interest of this study is the fully vaccinated group with at least 14 days between their second dose and the diagnostic test.

We did several subanalyses. Firstly, we split data according to the study period (on 25 December 2021) considering the change in the dominant variant (from delta to omicron). In the last week of the delta period, 68.2% of cases were identified as due to delta and 31.7% as due to omicron. During the first week of the omicron period, 79.2% of the studied cases were assigned to this variant.²² For a second subanalysis, we used another split in age subgroups (3-11 and 12-17 years).

Seeking evidence of waning immunity, in a third subanalysis we divided the fully vaccinated group into four levels according to the time between their second dose and the test (15-30, 31-45, 46-60, ≥ 61 days). For a fourth subanalysis, we split the same level to assess vaccine effectiveness by product in the adolescent subpopulation, with all possible combinations of BNT162b2 and mRNA-1273 vaccines against both variants.

Fifthly, we did three sensitivity analyses. We assessed the effect of the type of test in the estimation by doing a subanalysis estimating RT-PCR and antigen based vaccine effectiveness separately. We fitted a linear regression model and used the non-parametric Mann-Whitney-Wilcoxon test to assess whether the difference between estimations was different from zero. For the linear model, PCR based estimates were the predictor variable and antigen based estimates were the dependent variable, as most test negative, case-control studies use PCR tests to assign participants a case status. We then repeated the main analysis excluding matching pairs in epidemiological weeks with zero fully vaccinated, to assess how not

holding the positivity assumption might bias our estimates. Lastly, we excluded participants who had a previous infection to assess whether these participants might be biasing our estimates.

Finally, for a fatality analysis, we matched participants with covid-19 associated death one to four to covid-19 negative participants by using the same matching criteria as the one used in the primary analysis estimating vaccine effectiveness against SARS-CoV-2 infection. On this second matched case-control group, we estimated vaccine effectiveness against mortality through an adjusted conditional logistic regression model.

Data preprocessing was carried out with PostgreSQL (PostgreSQL Global Development Group). We used R software (R Development Core Team, version 3.6.1) for all statistical analyses.

Public and patient involvement

This was an unfunded study using routine surveillance data sources. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to directly disseminate the results of the research to study participants.

Results

The initial case-control cohort included 844 460 participants, of whom 421 359 sought RT-PCR testing and 423 101 were tested with immunoassays for antigen detection, between 12 September 2021 and 23 April 2022. Those who tested positive (231 181) had a higher proportion of reported comorbidities (5.2% *v* 4.9%; $P < 0.001$), were less likely to be male (47.4% *v* 50.7%; $P < 0.001$), had sought to be tested in more advanced epidemiological weeks and were more frequently tested with antigen detection (65.4% *v* 44.3%; $P < 0.001$)

(supplementary table A). Furthermore, they were slightly older (mean age 11.9 v 10.8 years; $P < 0.001$) and had significant differences in the regional distribution (supplementary table B).

After matching, 139 321 (60.3%) of 231 181 cases with their corresponding controls remained for analysis. As a result of exact matching on presence of comorbidities, sex, type of test, province (supplementary table C), and week of testing, the distribution of those variables in cases and controls are equal. Age was matched with a tolerance of 1 year, yielding non-significant differences between the two groups ([table 1](#)).

Table 1

Population characteristics after matching, by test result and vaccination status. Values are numbers (percentages) unless stated otherwise

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The fully vaccinated participants represented 54% (150 966/278 642) of the matched case study group. Of these fully vaccinated participants, 73 409 (48.6%) were included as cases and the remainder as controls. In the 12-17 year old fully vaccinated subgroup, 86 338/91 108 (94.8%) received a homologous two dose schedule (64 197 (70.5%) BNT162b2; 22 141 (24.3%) mRNA-1273) and 4770 (5.2%) received a heterologous one (4197 (4.6%) mRNA-1273 and then BNT162b2; 573 (0.6%) BNT162b2 and then mRNA-1273). All children (3-11 years old) included as fully vaccinated received a two dose schedule of BBIBP-CorV ([table 2](#)). The median time from second dose to test was 66 (interquartile range 40) days for the 12-17 year old subgroup and 54 (32) days for the 3-11 year old subgroup.

Table 2

Vaccination schedule and vaccine effectiveness against infection, by combination and period. Values are numbers (percentages) unless stated otherwise

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Primary analysis on vaccine effectiveness in preventing infection

Figure 3 shows vaccine effectiveness in preventing infection according to the predominant variant and age group. Vaccine effectiveness was considerably higher in all age groups when we analysed only the period of delta variant predominance. Vaccine effectiveness was 64.2% (95% confidence interval 61.6% to 66.5%) for all ages, 61.2% (56.4% to 65.5%) for children (3-11 years), and 66.8% (63.9% to 69.5%) for adolescents (12-17 years). Estimates of vaccine effectiveness decreased markedly during the period of omicron predominance. Vaccine effectiveness was 19.9% (18.0% to 21.8%) for all ages, with a slightly higher value in adolescents who received mRNA based vaccines (26.0%, 23.2% to 28.8%) than in children who received BBIBP-CorV (15.9%, 13.2% to 18.6%). Assessment of robustness by means of bootstrapping yielded almost identical results with narrower confidence intervals (supplementary table D).

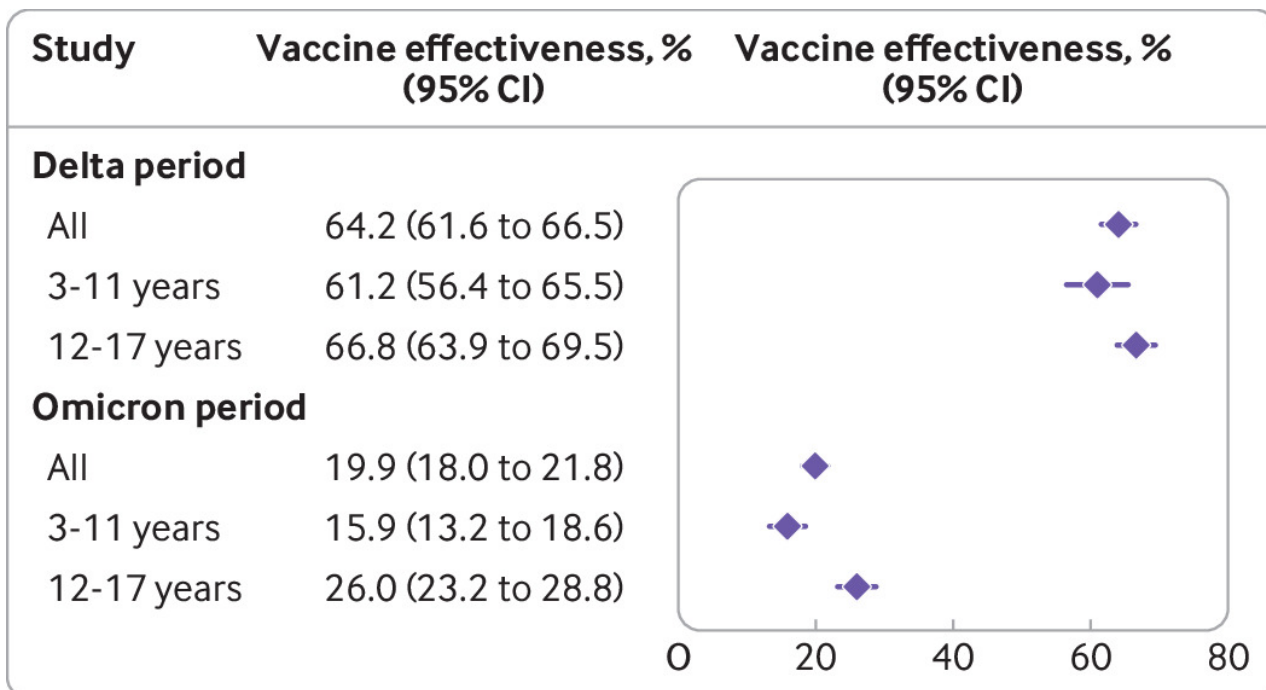


Fig 3
 Vaccine effectiveness of two dose schedules against SARS-CoV-2 infection, by age group and study period. CI=confidence interval

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Waning immunity

As shown in [figure 4](#), during the delta period, vaccine effectiveness declined according to time since vaccination from 68.4% (64.1% to 72.2%) at 15-30 days to 65.2% (44.0% to 78.4%) at ≥ 61 days in children and from 74.8% (71.3% to 77.9%) to 56.3% (50.2% to 61.7%) in adolescents (supplementary table E). During the omicron period, the initial effectiveness was lower and the decline over time was steeper. Vaccine effectiveness dropped from 37.6% (34.2% to 40.8%) to 2.0% (1.8% to 5.6%) in children and from 55.8% (52.4% to 59.0%) to 12.4% (8.6% to 16.1%) in the adolescent subpopulation.

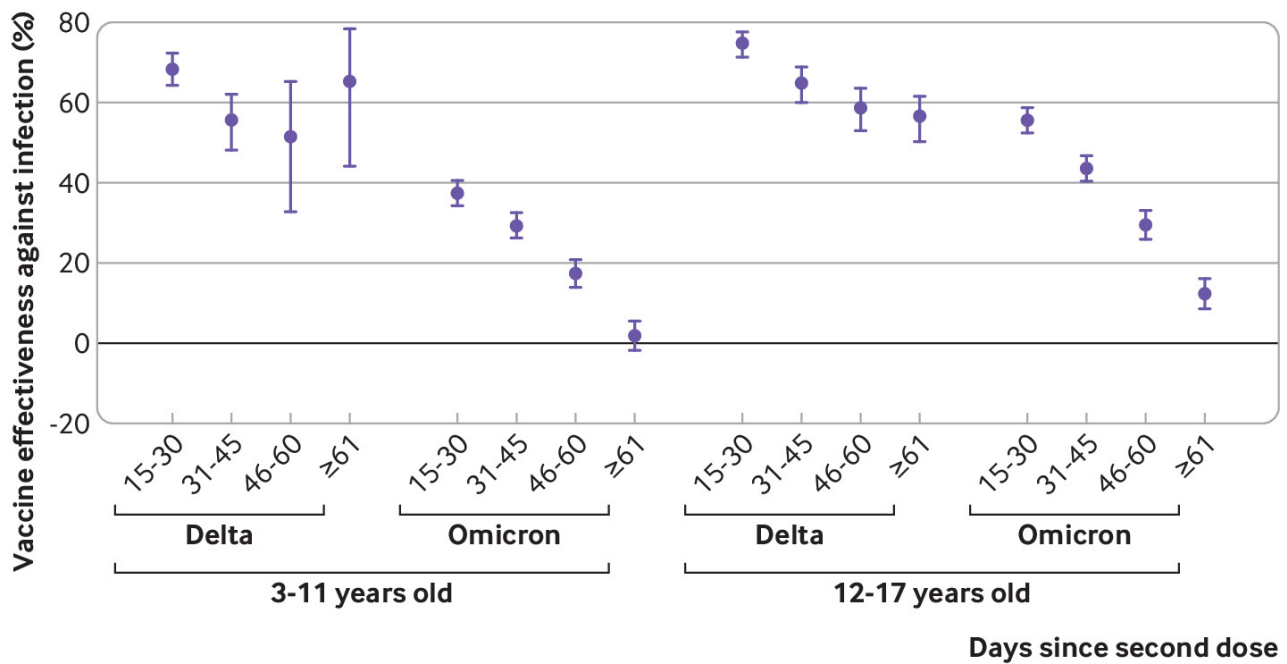


Fig 4
Vaccine effectiveness (with 95% confidence interval) of two dose schemes against SARS-CoV-2 infection, by age group, study period, and days since second dose

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Subanalysis by vaccine type (adolescents)

As shown in [table 2](#), all combinations of mRNA vaccine products showed similar results in adolescents. During the delta period, vaccine effectiveness was 70.2% (66.8% to 73.1%) for the homologous schedule of mRNA-1273 and 64.1% (60.5% to 67.3%) for BNT162b2. The heterologous schedule of mRNA-1273 then BNT162b2 yielded a vaccine effectiveness of 66.3% (54.0% to 75.4%), and that for BNT162b2 then mRNA-1273 was 88.9% (66.1% to 96.4%). In the omicron period, homologous schedules of mRNA-1273 and BNT162b2 showed a vaccine effectiveness of 17.9% (14.0% to 21.5%) and 28.1% (25.2% to 30.8%), respectively. Heterologous schedules showed 40.6% (29.4% to 50.0%) for participants receiving the BNT162b2 vaccine first and 31.5% (26.3% to 36.4%) for those who received the mRNA-1273 vaccine first.

Sensitivity analyses

On the hypothesis that estimations might be affected by the type of test used to select cases and controls, we analysed the results for RT-PCR and antigen test based vaccine effectiveness estimates (supplementary table F). The slope for the linear regression between RT-PCR and antigen based estimates of vaccine effectiveness was 0.933 (95% confidence interval 0.892 to 0.974), showing that antigen based vaccine effectiveness estimates tend to be slightly lower than RT-PCR based estimates, rejecting the null hypothesis that the slope equals one ($P=0.004$) (supplementary figure A). Additionally, we did a Mann-Whitney-Wilcoxon test to assess the relative width of the confidence interval between the two techniques. It yielded a non-significant P value of 0.61.

To evaluate how not holding the positivity assumption could affect our estimations, we did a sensitivity analysis excluding matching pairs in epidemiological weeks with zero fully vaccinated participants for each age subgroup. This occurred only during the delta period, and for both age groups the confidence intervals had a wide overlap with the results reported in the main analysis (supplementary table G).

Next, we did a sensitivity analysis excluding participants with previous infection to evaluate whether our estimates might be biased due to previously acquired immunity. After exclusion of participants who fulfilled this criterion, vaccine effectiveness estimates had a wide overlap with the results reported in the main analysis (supplementary table H).

Vaccine effectiveness in preventing mortality

Fifty one deaths related to covid-19 were notified among cases, of which seven occurred in the delta period (all in unvaccinated participants). Of the 51, 30 were unvaccinated participants (16 children; 14 adolescents), eight were partially vaccinated (three children; five adolescents), nine were fully vaccinated (six children;

three adolescents), and four had other status (two children; two adolescents). Two further deaths were excluded after validation that the cause of death was not related to covid-19. Following one-to-four case-control matching, 44 (90%) of 49 deceased participants were successfully matched ([table 3](#)). After adjusting a conditional logistic regression model, we found that vaccine effectiveness against mortality in the 3-17 year old group for the two dose schedule was 89.3% (73.9% to 95.6%). When we considered only the omicron period, vaccine effectiveness remained high at 88.1% (70.7% to 95.2%). Considering age subgroups, vaccine effectiveness against death related to SARS-CoV-2 infection during omicron predominance was 97.6% (81.0% to 99.7%) for adolescents and 66.9% (6.4% to 89.8%) for children.

Table 3

Characteristics of covid-19 related deaths and matched controls. Values are numbers (percentages) unless stated otherwise

- [View popup](#)
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Discussion

This study provides real world evidence for the effectiveness of mRNA-1273, BNT162b2, and BBIBP-CoV vaccines in preventing infection and mortality in children and adolescents in Argentina. To our knowledge, this is one of the first studies that reports vaccine effectiveness in children under 5 years old, in addition to evaluation of mortality and analysis of waning for BBIP-CoV and mRNA-1273 vaccines. Our results suggest that the primary vaccination schedule is effective in preventing mortality in children and adolescents with covid-19 regardless of the circulating SARS-CoV-2 variant. Vaccine effectiveness in preventing mortality in children vaccinated with BBIP-CoV was lower than in adolescents vaccinated with mRNA vaccines; however, owing to the scarcity of events, analysis of mortality by age group yielded results with wide confidence intervals.

Our estimates also suggest that two doses of vaccine are effective in preventing SARS-CoV-2 infection in children and adolescents in the short term. Vaccine effectiveness was considerably higher when delta was the predominant circulating variant, but a significant decrease was observed over time, especially during omicron predominance.

Comparison with other studies

By the time of our study, only BBIBP-CorV was indicated in children, so we could not compare vaccine effectiveness in children by vaccine type. Evidence is variable taking into consideration that published studies differ in age groups and time to vaccination periods. Nevertheless, BNT162b2 vaccine effectiveness in preventing infection during omicron predominance has been evaluated, with vaccine effectiveness between 29.4% and 51% being reported.¹²²³²⁴ These results are similar to the vaccine effectiveness reported in our study and in other studies that evaluated inactivated vaccines (CoronaVac) and reported vaccine effectiveness of 39.8% and 38.2%.¹⁶¹⁸

In adolescents, we evaluated different vaccine schedules. Compared with the delta period, vaccine effectiveness during the omicron period was lower for both evaluated schedules (homologous and heterologous), in consistency with the literature. A previous study of immunogenicity in adults in Argentina evaluated heterologous schedules of adenoviral vectored, inactivated, and mRNA vaccines and endorsed heterologous vaccination strategies.²⁵ In our study, which evaluated mRNA-1273 and BNT162b2 vaccines, heterologous schedules showed a comparable to superior vaccine effectiveness in comparison with homologous schedules. Nevertheless, further investigation may be needed to evaluate different vaccine schedules.

In addition, our results are consistent with other published studies that found high short term protection induced by the primary vaccination regimen against SARS-CoV-2 infection during the delta predominance period.²⁶²⁷²⁸ However, since the emergence and

spread of the omicron variant of concern, a reduction in vaccine effectiveness in preventing infection has been observed in adults and children.^{1329,30,31} A population based study in Norway reported that one and two doses of mRNA vaccine (BNT162b2) in adolescents protected against infection with the delta variant, reaching an effectiveness of 91% after the primary vaccination schedule and declining to 53% for the omicron variant.²⁸ Fowlkes and colleagues described a decrease in vaccine effectiveness against infection in adolescents for the primary mRNA vaccine series (BNT162b2) from 87% to 59%, comparing delta and omicron variants.¹² In Chile, Jara and colleagues reported vaccine effectiveness in preventing infection for a complete schedule of inactivated vaccine (Sinovac's CoronaVac) in 6-11 year old children of 75.8% during the delta circulating period. In another study, Jara and colleagues reported a lower vaccine effectiveness of 38.2% during omicron circulation for the same vaccine in 3-5 year old children.^{15,16} Vaccine effectiveness reported by Jara and colleagues is similar to that observed with BBIBP-CorV in children in our study.

Available evidence suggests that the vaccine induced immune response could decrease over time, with a reduction in the effectiveness of SARS-CoV-2 vaccines in preventing infection, particularly in the context of the emergence of new variants of the virus with potential ability to partially evade the host immune response.^{32,33} Our results highlight not only a decrease in effectiveness when comparing delta with omicron but also, and especially during omicron predominance, a significant decrease with time since vaccination. The decrease observed with BBIBP-CorV in children in our study is consistent with published evidence. Fleming-Dutra and colleagues did a test negative, case-control analysis to evaluate the vaccine effectiveness of BNT162b2 in preventing infection among children and adolescents during omicron variant predominance and reported that two months after the second dose the estimated vaccine effectiveness had declined in both age groups.³⁴ Similarly, Dorabawila and colleagues concluded that the

risk of infection and hospital admission was higher in unvaccinated children and adolescents, although the protection declined over time from vaccination.³⁰ Sacco and colleagues reported a decrease in vaccine effectiveness for BNT162b2 in preventing infection over time, and Klein and colleagues found no evidence of protection for adolescents aged 12-17 years after receipt of two doses of BNT162b2 ≥ 150 days earlier during omicron predominance.^{23,29} In a Norwegian study, protection against omicron after a complete primary regimen in adolescents was reduced to 23% from 63 days post-vaccination, whereas a smaller reduction was documented for delta.²⁸ Amir and colleagues observed a rapid reduction in protection against omicron of two doses of mRNA vaccine (BNT162b2) in adolescents aged 12-15, with an increase in the rate of confirmed infections from 60 days after the second dose.³⁵ Evidence of a decrease in vaccine effectiveness after inactivated vaccines is lacking.

Although the previously cited studies suggest a reduction in vaccine effectiveness for SARS-Cov-2 infection over time, observational studies have shown that vaccine effectiveness against severe disease is higher and more stable. Data from Brazil and Scotland in adolescents aged 12-17 years during the omicron wave showed a reduction in BNT162b2 vaccine effectiveness for symptomatic infection from 98 days after receipt of the primary schedule. However, protection against hospital admission and death with covid-19 remained above 80% in the same time interval.³⁶ In Canada, vaccine effectiveness for two doses of BNT162b2 against severe disease with omicron in the same age group was 85%, with a stable trend over time.³⁷ In children, Tan and colleagues reported a vaccine effectiveness of 82.7% in preventing hospital admission for BNT162b2.³⁸ For inactivated vaccines, vaccine effectiveness of 59.2% and 64.6% have been reported for prevention of hospital admission with Sinovac's CoronaVac.^{16,18}

Our results are consistent with a study conducted in Buenos Aires Province (Argentina) that reported a two dose vaccine effectiveness of 78.0% for hospital admission in 3-17 year olds evaluated during delta/omicron circulation.¹⁷ As expected, we found that vaccine effectiveness for infection was lower and vaccine effectiveness for mortality was higher than these estimations for protection against hospital admissions, especially in adolescents. In this study, estimated effectiveness against hospital admissions was higher when delta was predominant, although it remained higher than 65% during the omicron period.¹⁷ This study, which took place in an Argentinian province, was the first one to evaluate vaccine effectiveness of BBIBP-CorV in children between 3 and 11 years old. However, it did not evaluate vaccine effectiveness in preventing infection or mortality or decrease in vaccine effectiveness over time.¹⁷

Our study evaluated vaccine effectiveness in children and adolescents, including different types of diagnostic tests. Although statistically significant, the real life implications of these differences might not be important for public health agents. According to our results, antigen based estimates tended to be 6.7% lower ($P=0.004$) than the PCR based one for the same population and provide results with a comparable variance. Therefore, the advantages of using antigen tests alone or in addition to RT-PCR tests in vaccine effectiveness studies would outweigh the slight differences in estimations. Tan and colleagues reported differences in vaccine effectiveness by type of diagnostic test; however, they highlighted that in disease management protocols, the country included PCR testing for people with more severe symptoms or coexisting conditions, so they used PCR results as proxy of increased severity of illness.³⁸

Strengths and limitations of study

The study has several strengths. Firstly, the sample size was large and included all children and adolescents tested and reported to the National Surveillance System in Argentina during the study period. Secondly, the high quality of the epidemiological surveillance (especially for laboratory and mortality data) and vaccination records used confers robustness to the results.

Limitations of our study include that some information, such as symptoms and hospital admissions, was incomplete and was consequently not included in any analysis. Also, as persistent potential confounders, misclassification, or selection bias might have been present, we decided to minimise them by matching with strict criteria on all the available confounders and doing univariate conditional logistic regression analyses. We also did several sensitivity analyses to assess the effect of some unmeasured phenomena. Nevertheless, unobserved confounding might exist and bias odds ratio estimations. The generalisability of our results is limited to the subpopulation who had access to testing. Additionally, as misclassification might have occurred as a result of non-100% specificity and sensitivity of covid-19 tests, we included a sensitivity analysis to assess how test related problems might affect the vaccine effectiveness estimations, which showed that antigen based estimates of vaccine effectiveness tended to be lower. Other limitations include that each age group used different vaccines, so any conclusion based on their differences should not be attributed exclusively to the vaccine technology or to age related factors. Finally, information about variants could not be established at an individual level, and we used the prevalent variant from surveillance data when analysing our results.

Conclusions

Vaccine effectiveness remained high for preventing mortality in children and adolescents regardless of the predominant circulating variant. Vaccines were effective in preventing SARS-CoV-2 infection in the short term after vaccination, being lower when the omicron

variant was predominant and decreasing sharply over time. Heterologous mRNA schedules showed comparable to superior vaccine effectiveness in comparison with homologous schedules. In summary, vaccinating children is an important public health measure that will prevent mortality in this population, especially in periods of high viral circulation.

What is already known on this topic

- mRNA and inactivated covid-19 vaccines are effective in preventing severe disease and infection in children and adolescents in the short term after vaccination, but data on mortality are lacking
- Waning of protection against infection has been described, especially for mRNA vaccines, but evidence for inactivated vaccines in children is limited

What this study adds

- Vaccine effectiveness remained high for preventing mortality in children and adolescents aged 3-17 years, regardless of the predominant circulating variant
- Waning of protection against infection was described and evaluated for both types of vaccines
- Heterologous mRNA schedules showed comparable to superior vaccine effectiveness in comparison with homologous schedules

Ethics statements

Ethical approval

Covid-19 surveillance was included as an obligatory notifiable disease by RM 680/2020

(<https://www.boletinoficial.gob.ar/detalleAviso/primera/227324/20200331>). As secondary data were used, the study protocol was subject to an internal review by the ethical area of the Research

Department of the Ministry of Health and was found to be fully compliant with all regulatory requirements. As no regulatory issues were identified, a full ethical review was deemed not to be necessary.

Data availability statement

The data that support the findings of this study will be available for researchers who provide a methodologically sound proposal after it is approved, on request from the corresponding author.

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Footnotes

- Contributors: AR, CV, and JMC conceived and supervised the study. AR was in charge of the project administration. AR and SO designed the methods. SO performed and interpreted the formal analysis. AR, SO, CV, MDVJ, MP, MEC, MP, and ANI conceptualised the study and wrote the original draft. CMG critically revised the manuscript. MPB, MBM, and ML developed the supporting algorithms and curated the data. All authors reviewed, edited and gave final approval for the version to be submitted. AR is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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- The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.
- Dissemination to participants and related patient and public communities: Results from this research will be shared through conferences with expert immunisation advisory committees for Argentina and public health officials overseeing Argentina's covid-19 immunisation campaign. The findings will also be further disseminated through the National Health Ministry website, social media channels, and news media.
- Provenance and peer review: Not commissioned; externally peer reviewed.

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