Protection against symptomatic infection with delta (B.1.617.2) and omicron (B.1.1.529) BA.1 and BA.2 SARS-CoV-2 variants after previous infection and vaccination in adolescents in England, August, 2021–March, 2022: a national, observational, test-negative, case-control study

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Summary

Background Little is known about protection against SARS-CoV-2 infection following previous infection with specific individual SARS-CoV-2 variants, COVID-19 vaccination, and a combination of previous infection and vaccination (hybrid immunity) in adolescents. We aimed to estimate protection against symptomatic PCR-confirmed infection with the delta (B.1.617.2) and omicron (B.1.1.529) variants in adolescents with previous infection, mRNA vaccination, and hybrid immunity.

Methods We conducted an observational, test-negative, case-control study using national SARS-CoV-2 testing and COVID-19 mRNA vaccination data in England. Symptomatic adolescents aged 12–17 years who were unvaccinated or had received primary BNT162b2 immunisation at symptom onset and had a community SARS-CoV-2 PCR test were included. Vaccination and previous SARS-CoV-2 infection status in adolescents with PCR-confirmed COVID-19 (cases) were compared with vaccination and previous infection status in adolescents who had a negative SARS-CoV-2 PCR test (controls). Vaccination data were collected from the National Immunisation Management System, and were linked to PCR testing data. The primary outcome was protection against SARS-CoV-2 delta and omicron infection (defined as 1 – odds of vaccination or previous infection in cases divided by odds of vaccination or previous infection in controls).

Findings Between Aug 9, 2021, and March 31, 2022, 1 161 704 SARS-CoV-2 PCR tests were linked to COVID-19 vaccination status, including 390 467 positive tests with the delta variant and 212 433 positive tests with the omicron variants BA.1 and BA.2. In unvaccinated adolescents, previous SARS-CoV-2 infection with wildtype, alpha (B.1.1.7), or delta strains provided greater protection against subsequent delta infection (>86·1%) than against subsequent omicron infection (<52·4%); previous delta or omicron infection provided similar protection against omicron reinfection (52·4% [95% CI 50·9–53·8] *vs* 59·3% [46·7–69·0]). In adolescents with no previous infection, vaccination provided lower protection against omicron infection than against delta infection, with omicron protection peaking at 64·5% (95% CI 63·6–65·4) at 2–14 weeks after dose two and 62·9% (60·5–65·1) at 2–14 weeks after dose three, with waning protection after each dose. Adolescents with hybrid immunity from previous infection and vaccination had the highest protection, irrespective of the SARS-CoV-2 strain in the primary infection. The highest protection against omicron infection was observed in adolescents with vaccination and previous omicron infection, reaching 96·4% (95% CI 84·4–99·1) at 15–24 weeks after vaccine dose two.

Interpretation Previous infection with any SARS-CoV-2 variant provided some protection against symptomatic reinfection, and vaccination added to this protection. Vaccination provides low-to-moderate protection against symptomatic omicron infection, with waning protection after each dose, while hybrid immunity provided the most robust protection. Although more data are needed to investigate longer-term protection and protection against infection with new variants, these data question the need for additional booster vaccine doses for adolescents in populations with already high protection against SARS-CoV-2 infection.

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Introduction

Adolescents have a lower risk of severe or fatal COVID-19 than adults.[1] Consequently, in England and elsewhere, from December, 2020, the roll-out of COVID-19 vaccines prioritised older adults, health-care workers, and adults at high risk of severe disease. In young people, early reports of rare but potentially severe myocarditis following mRNA vaccination led the UK Joint Committee

Research in context

Evidence before this study

We searched PubMed and preprint servers SSRN and medRxiv on Sept 22, 2022, from Jan 1, 2020, to Sept 8, 2022, for papers in English, using the terms ("SARS-CoV-2" or "COVID-19") AND ("effectiveness" or "hybrid immunity" or "protection" or "waning" or "reinfection") AND ("delta" or "omicron") in the title or abstract. Most previous studies focused on adults and showed high protection from previous SARS-CoV-2 infection against reinfection with pre-omicron variants, but lower protection against reinfection with omicron (B.1.1.529) variants, with hybrid immunity providing the most robust protection. We have previously reported COVID-19 vaccine effectiveness in adolescents with no previous infection; however, there are limited data on the protection offered by infection with specific individual SARS-CoV-2 variants, and the added protection from vaccination, in adolescents with previous infection.

Added value of this study

Using national SARS-CoV-2 testing and COVID-19 mRNA vaccination data in England, we were able to estimate protection associated with previous SARS-CoV-2 infection, mRNA vaccination, and hybrid immunity from previous infection plus vaccination, using a test-negative, case-control design against PCR-confirmed symptomatic COVID-19. We found that protection against symptomatic infection with the delta (B.1.617.2) variant was greater than protection against symptomatic omicron infection in adolescents who had previous infection with wild-type, alpha (B.1.1.7), or delta variants. Similar trends were observed in vaccinated adolescents with no previous infection. Previous omicron infection together with vaccination provided the greatest protection against omicron variant infection.

Implications of all the available evidence

Previous SARS-CoV-2 infection with any variant provides some protection against reinfection, and COVID-19 mRNA vaccination also provides some protection. Our findings show, for the first time in adolescents, the additional protection afforded by hybrid immunity. In the context of the waves of omicron infections in the UK, our findings provide important evidence of only modest short-term protection against mild disease with omicron variant infection following vaccination, which has implications for the consideration of future adolescent COVID-19 vaccination and booster programmes.

on Vaccination and Immunisation (JCVI) to recommend only one dose of mRNA vaccine for people aged 16–17 years from Aug 4, 2021, and recommend against vaccinating healthy people aged 12–15 years, as the margin of benefit was deemed too small to support universal vaccination in this age group.[2,3] Ministers were, however, advised to seek guidance in evaluating the wider national context, which was outside the JCVI's remit. An expert group recommended universal vaccination of people aged 12–15 years, to prevent educational disruption, from Sept 13, 2021.[4] A second vaccine dose was subsequently recommended for both age groups, to be given at 8–12 weeks after the first dose, which is consistent with the UK recommendation for adult vaccination.[5] By March 31, 2022, in England, 63·6% of people aged 16–17 years and 48·2% of people aged 12–15 years had received at least one COVID-19 mRNA vaccine dose, 42·9% and 25·7% had received at least two doses, and 6·3% and 0·2% had received three doses, respectively.[6]

There have been multiple waves of SARS-CoV-2 infections in the UK since March, 2020, with new waves often following the emergence and rapid spread of new variants, including the alpha (B.1.1.7) variant in November, 2020, delta (B.1.617.2) in April, 2021, and omicron (B.1.1.529) in November, 2021. Delta was more transmissible than alpha[7] but, unlike in adults, it was not associated with more severe disease in children and adolescents.[8] The ability of the omicron BA.1 variant, identified in England in late November, 2021, and the BA.2 variant, identified in late December, 2021, to evade both natural and vaccine-induced immunity was associated with the highest case numbers to date across all age groups, although hospitalisation rates and deaths remained low,[9] which was likely to be due to immunity from a combination of previous infections and vaccination,[10] and because the omicron variant infects the upper airway rather than the lower airway and causes less severe disease.[11,12]

As in adults, we and others have shown a modest reduction in vaccine effectiveness over time against symptomatic delta disease in adolescents with no previous SARS-CoV-2 infection, and much lower vaccine effectiveness against symptomatic omicron disease, although protection against severe disease with both variants was higher after vaccination.[13,14] Studies have shown that adults with hybrid immunity from a combination of previous infection and vaccination had greater, longer-lasting protection against reinfection than unvaccinated adults with previous infection or adults with no previous infection who had received two or more COVID-19 vaccine doses.[15,16] Whether the same trends occur in adolescents, who are more likely than adults to remain asymptomatic or develop a mild illness when exposed to SARS-CoV-2, is not known.[1]

In England, SARS-CoV-2 PCR testing was freely available from June, 2020, to March, 2022. Given that around half of all adolescents have had at least one COVID-19 vaccine dose since September, 2021, together with high levels of community PCR testing, this provided

a unique opportunity to assess protection against SARS-CoV-2 infection in adolescents. We aimed to estimate protection against symptomatic PCR-confirmed infection with the delta and omicron BA.1 and BA.2 variants in adolescents with previous infection, mRNA vaccination, and hybrid immunity.

Methods

Study design and participants

We conducted an observational, test-negative, case-control study in England. We estimated protection against PCR-confirmed COVID-19 (symptomatic SARS-CoV-2 infection) after combinations of previous infection with wildtype, alpha, delta, and omicron variants of SARS-CoV-2 with one or two BNT162b2 (Comirnaty, Pfizer-BioNTech) doses or a booster dose of either BNT162b2 or mRNA-1273 (Spikevax, Moderna), during periods of delta or omicron BA.1 and BA.2 dominance (appendix p 1). Symptomatic adolescents aged 12–17 years who were unvaccinated, or had received primary BNT162b2 immunisation, at symptom onset and had a community (Pillar 2) SARS-CoV-2 PCR test were included. Vaccination status and previous SARS-CoV-2 infection status in participants with PCR-confirmed COVID-19 (cases) were compared with vaccination status and previous infection status in participants who had a negative SARS-CoV-2 PCR test (controls).

PCR testing data for adolescents were extracted on May 31, 2022, for tests taken from Aug 9, 2021, when routine vaccination uptake in people aged 16–17 years started to increase, to March 31, 2022, when community SARS-CoV-2 PCR testing ended. We accessed the National Immunisation Management System (NIMS) on May 31, 2022, to collect dates of vaccination and vaccine manufacturer, sex, date of birth, race or ethnic group, and residential address. More details on data sources and linkage are provided in the appendix (p 2).

The UK Health Security Agency has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information under Section 3 for national surveillance of communicable diseases and, as such, individual informed consent was not required to access patient records.

Procedures

Previous infection was defined as PCR-confirmed SARS-CoV-2 infection at least 90 days before current sample date. Negative tests taken within 7 days of a previous negative test, and negative tests where the symptom onset date was within the 10 days of a symptom onset date for a previous negative test, were excluded as these were likely to represent the same episode. Negative tests taken within 21 days of a subsequent positive test were excluded as these were thought to possibly be false negative results. Positive and negative tests within 90 days of a previous positive test were excluded; however, where participants had later positive tests within 14 days of a positive test, then preference was given to PCR tests and tests associated with symptomatic infection. For adolescents who had more than one negative test, a maximum of two negative tests could be included per

	Overall (n=1 161 704)	Negative (n=558 804)	Positive delta infection (n=390 467)	Positive omicron infection (n=212 433)
Vaccination status and interval after vaccine				
Unvaccinated	703 582 (60·6%)	307 538 (55·0%)	309 246 (79·2%)	86 798 (40·9%)
Dose one, Pfizer				
0–1 week	59 908 (5·2%)	25 421 (4·5%)	30 793 (7·9%)	3694 (1·7%)
2–14 weeks	258 621 (22·3%)	146 537 (26·2%)	45 557 (11·7%)	66 527 (31·3%)
15–24 weeks	24 043 (2·1%)	10 197 (1·8%)	1513 (0·4%)	12 333 (5·8%)
25–39 weeks	1239 (0·1%)	515 (0·1%)	46 (<0·1%)	678 (0·3%)
≥40 weeks	60 (<0·1%)	25 (<0·1%)	1 (<0·1%)	34 (<0·1%)
Dose two, Pfizer				
0–1 week	21 022 (1·8%)	12 272 (2·2%)	1112 (0·3%)	7638 (3·6%)
2–14 weeks	70 504 (6·1%)	43 548 (7·8%)	948 (0·2%)	26 008 (12·2%)
15–24 weeks	10 121 (0·9%)	6127 (1·1%)	906 (0·2%)	3088 (1·5%)
25–39 weeks	3891 (0·3%)	1937 (0·3%)	305 (0·1%)	1649 (0·8%)
≥40 weeks	185 (<0·1%)	72 (<0·1%)	1 (<0·1%)	112 (0·1%)
Booster dose, any vaccine				
0–1 week	2407 (0·2%)	1263 (0·2%)	30 (<0·1%)	1114 (0·5%)
2–14 weeks	5809 (0·5%)	3229 (0·6%)	9 (<0·1%)	2571 (1·2%)
15–24 weeks	308 (<0·1%)	122 (<0·1%)	..	186 (0·1%)
Age, years				
12	210 409 (18·1%)	98 447 (17·6%)	74 813 (19·2%)	37 149 (17·5%)
13	214 264 (18·4%)	101 187 (18·1%)	76 533 (19·6%)	36 544 (17·2%)
14	212 474 (18·3%)	100 718 (18·0%)	75 341 (19·3%)	36 415 (17·1%)
15	210 943 (18·2%)	97 263 (17·4%)	78 017 (20·0%)	35 663 (16·8%)
16	151 286 (13·0%)	76 181 (13·6%)	43 941 (11·3%)	31 164 (14·7%)
17	162 328 (14·0%)	85 008 (15·2%)	41 822 (10·7%)	35 498 (16·7%)
Gender				
Female	597 530 (51·4%)	282 218 (50·5%)	200 042 (51·2%)	115 270 (54·3%)
Male	562 279 (48·4%)	275 608 (49·3%)	189 875 (48·6%)	96 796 (45·6%)
Missing	1895 (0·2%)	978 (0·2%)	550 (0·1%)	367 (0·2%)
Ethnicity				
Asian	139 768 (12·0%)	68 172 (12·2%)	40 735 (10·4%)	30 861 (14·5%)
Black	26 865 (2·3%)	10 963 (2·0%)	7853 (2·0%)	8049 (3·8%)
Mixed	23 670 (2·0%)	11 098 (2·0%)	7507 (1·9%)	5065 (2·4%)
White	927 923 (79·9%)	447 602 (80·1%)	321 873 (82·4%)	158 448 (74·6%)
Other	5646 (0·5%)	2644 (0·5%)	1637 (0·4%)	1365 (0·6%)
Missing	37 832 (3·3%)	18 325 (3·3%)	10 862 (2·8%)	8645 (4·1%)
National Health Service region				
East of England	145 303 (12·5%)	70 630 (12·6%)	49 130 (12·6%)	25 543 (12·0%)
London	123 507 (10·6%)	59 183 (10·6%)	34 369 (8·8%)	29 955 (14·1%)
Midlands	229 938 (19·8%)	110 088 (19·7%)	80 117 (20·5%)	39 733 (18·7%)
North east	180 946 (15·6%)	86 604 (15·5%)	61 554 (15·8%)	32 788 (15·4%)
North west	152 634 (13·1%)	75 237 (13·5%)	47 774 (12·2%)	29 623 (13·9%)
South east	200 411 (17·3%)	95 014 (17·0%)	69 872 (17·9%)	35 525 (16·7%)
South west	128 958 (11·1%)	62 045 (11·1%)	47 648 (12·2%)	19 265 (9·1%)
Missing	7 (<0·1%)	3 (<0·1%)	3 (<0·1%)	1 (<0·1%)

(Table 1 continues on next page)

See Online for appendix

For more on **Regulation 3** see https://www.legislation.gov.uk/uksi/2002/1438/regulation/3/made

	Overall (n=1 161 704)	Negative (n=558 804)	Positive delta infection (n=390 467)	Positive omicron infection (n=212 433)
(Continued from previous page)				
Index of Multiple Deprivation quintile				
1	224 588 (19·3%)	108 095 (19·3%)	68 298 (17·5%)	48 195 (22·7%)
2	208 491 (17·9%)	98 776 (17·7%)	67 945 (17·4%)	41 770 (19·7%)
3	222 041 (19·1%)	105 869 (18·9%)	76 538 (19·6%)	39 634 (18·7%)
4	236 945 (20·4%)	114 135 (20·4%)	82 895 (21·2%)	39 915 (18·8%)
5	267 097 (23·0%)	130 688 (23·4%)	93 971 (24·1%)	42 438 (20·0%)
Missing	2542 (0·2%)	1241 (0·2%)	820 (0·2%)	481 (0·2%)
Vaccine priority groups				
At risk	80 056 (6·9%)	44 684 (8·0%)	20 857 (5·3%)	14 515 (6·8%)
Clinically extremely vulnerable	1802 (0·2%)	1132 (0·2%)	264 (0·1%)	406 (0·2%)
Previous SARS-CoV-2 infection				
No	1 046 816 (90·1%)	477 150 (85·4%)	385 967 (98·8%)	183 699 (86·5%)
Yes	114 888 (9·9%)	81 654 (14·6%)	4500 (1·2%)	28 734 (13·5%)

Data are n (%).

Table 1: **Characteristics of SARS-CoV-2 PCR test results among adolescents aged 12–17 years**

	Protection against delta	Protection against omicron
Previous infection with wildtype	87·6% (86·8–88·4)	32·7% (27·7–37·4)
Previous infection with alpha	86·1% (85·4–86·8)	36·6% (32·9–40·1)
Previous infection with delta	92·3% (91·7–92·9)	52·4% (50·9–53·8)
Previous infection with omicron	..	59·3% (46·7–69·0)

Data are point estimate (95% CI).

Table 2: **Protection associated with previous infection by variant against symptomatic SARS-CoV-2 infection with the delta and omicron BA.1 and BA.2 variants in unvaccinated adolescents**

person, one from before Nov 22, 2021, and one after Nov 22 (before and after omicron emergence, respectively). Data were restricted to people who reported symptoms and gave a symptom onset date within the 10 days before testing to account for reduced PCR sensitivity beyond this period.

The variant responsible for each case was defined according to whole genome sequencing, genotyping, S-gene target failure (SGTF) status, or time period, with sequencing taking priority, followed by genotyping followed by SGTF status, as described previously.[17,18] Where subsequent positive tests within 14 days included sequencing, genotyping, or SGTF information, this information was also used to classify the variant. S target-negative status was used to define the omicron variant when it was responsible for at least 80% of S target-negative cases (from Nov 29, 2021, onwards). From Jan 10, 2022, delta cases were identified by sequencing and genotyping only because the positive predictive value of S target-negative status to identify the delta variant had decreased and could no longer be used. Tests were defined as delta where there was no SGTF, sequencing, or genotyping test done until Nov 28, 2021, (delta dominant period), and as omicron where there was no such test done from Jan 5, 2022 (omicron dominant period). Positive tests with no sequencing, genotyping, or SGTF between Nov 29, 2021, and Jan 4, 2022, were excluded as these could be omicron or delta (appendix p 3). Omicron included BA.1 and BA.2 subvariants, which were both circulating widely during the study period. We did not separate BA.1 and BA.2 in our analysis because both subvariants appeared in quick succession over a short time period (appendix p 3),[19] and our previous analysis of real-world data showed similar vaccine effectiveness, and vaccine effectiveness rate of decline over time between the subvariants in adults.[20]

The variant of previous infection was assigned only on the basis of the period when each variant was most common based on sequencing (see appendix p 2 for details on positive predictive values). Wildtype was assumed for the period before Dec 8, 2020, alpha for Dec 8, 2020–May 9, 2021, delta for May 10, 2021–Dec 12, 2021, and omicron from Dec 13, 2021, onwards. When considering previous infections, for participants with more than one previous positive test, the first positive test was used.

Statistical analysis

We performed logistic regression, with the PCR test result as the dependent variable and vaccination status as an independent variable. The primary outcome was protection against SARS-CoV-2 delta and omicron infection, defined as 1 – odds of vaccination or previous infection in cases divided by odds of vaccination or previous infection in controls, with vaccination stratified by time interval after each dose and previous variant infection. The protection from combinations of vaccination and previous infection was adjusted for in logistic regression models for age, sex, index of multiple deprivation quintile, ethnic group, geographical region (National Health Service region), period (calendar week of test), clinical risk group status (a separate flag for those aged 16 years or older and younger than 16 years), and clinically extremely vulnerable (if aged 16 years or older). Age was defined as age at Aug 31, 2021. Vaccination periods considered after each dose were 0–1 week, 2–14 weeks, 15–24 weeks, 25–39 weeks, and 40 or more weeks. CIs were obtained from the logistic regression models using the estimated log-odds ratio and it's SE. Once an individual received a second or third vaccine dose they no longer contributed to time after a previous dose. For booster vaccination, data for BNT162b2 and mRNA-1273 vaccinations were combined. Previous infection status was determined relative to 7 days after the first vaccination dose, with people who had infection before this period regarded as having infection before vaccination, and those who had infection during or after this period regarded as having infection after vaccination (irrespective of timing of other doses).

	No previous infection	Previous wildtype infection before vaccination	Previous alpha infection before vaccination	Previous delta infection before vaccination	Previous delta infection after vaccination
Unvaccinated	..	87·6% (86·8–88·4)	86·1% (85·4–86·8)	92·3% (91·7–92·9)	92·3% (91·7–92·9)
Dose one, Pfizer					
0–1 week	8·5% (6·7–10·3)	92·6% (90·4–94·3)	90·3% (88·4–92·0)	91·3% (89·2–93·0)	..
2–14 weeks	59·4% (58·8–60·0)	98·1% (97·6–98·6)	95·5% (94·8–96·1)	97·5% (97·0–97·9)	95·2% (64·5–99·4)
15–24 weeks	23·5% (18·3–28·3)	98·6% (90·3–99·8)	94·2% (85·9–97·6)	99·0% (92·8–99·9)	98·4% (88·3–99·8)
25–39 weeks	57·4% (39·0–70·2)	..	..	..	..
≥40 weeks	..	..	..	..	..
Dose two, Pfizer					
0–1 week	71·0% (68·9–73·0)	..	98·4% (95·0–99·5)	99·6% (97·1–99·9)	94·2% (76·3–98·6)
2–14 weeks	91·8% (91·2–92·3)	98·8% (96·7–99·5)	99·2% (97·8–99·7)	98·7% (96·8–99·4)	..
15–24 weeks	80·9% (79·4–82·3)	98·6% (94·3–99·7)	97·0% (92·7–98·8)	..	98·3% (87·9–99·8)
25–39 weeks	71·9% (67·9–75·4)	94·8% (78·4–98·8)	97·3% (80·2–99·6)	..	96·4% (73·2–99·5)
≥40 weeks	..	..	..	..	..
Booster dose, any mRNA vaccine					
0–1 week	84·8% (77·6–89·7)	..	..	..	..
2–14 weeks	96·0% (92·2–97·9)	..	..	..	..
15–24 weeks	..	..	..	..	..

Data are point estimate (95% CI).

Table 3: **Protection from combinations of vaccination and previous infection with wildtype, alpha, and delta variants of SARS-CoV-2 against delta variant infection by time since vaccination**

Role of the funding source

There was no funding source for this study.

Results

Between Aug 9, 2021, and March 31, 2022, 1 161 704 PCR tests were linked to NIMS data for COVID-19 vaccination status, including 390 467 positive tests with the delta variant and 212 433 positive tests with the omicron variant (table 1; appendix pp 3–5). There was a match rate of 93% of tests in adolescents that could be linked to NIMS, including 93% for both cases and controls and 92–93% by age in years. Overall, there were 558 804 negative tests, including 460 756 during the delta period and 225 447 during the omicron period. Some negative tests could be used as controls for both delta and omicron periods. 597 530 (51·4%) tests were in female participants and 562 279 (48·4%) were in male participants, and 927 923 (79·9%) were in White participants (table 1).

In unvaccinated adolescents, protection against symptomatic delta infection was 87·6% (95% CI 86·8–88·4) after previous confirmed wildtype infection, 86·1% (85·4–86·8) after previous alpha infection, and 92·3% (91·7–92·9) after previous delta infection (table 2). Protection against symptomatic omicron infection was 32·7% (95% CI 27·7–37·4) after previous confirmed wildtype infection, 36·6% (32·9–40·1) after previous alpha infection, and 52·4% (50·9–53·8) after previous delta infection (table 2). Previous omicron infection was associated with protection of 59·3% (95% CI 46·7–69·0) against omicron reinfection, which was significantly lower than the protection associated with previous delta infection against delta reinfection.

Overall, mRNA vaccination protected against symptomatic delta infection in adolescents with no previous infection and provided additional protection in adolescents with previous infection. In adolescents with no previous infection, protection against delta after one vaccine dose was 59·4% (95% CI 58·8–60·0) after 2–14 weeks but decreased to 23·5% (18·3–28·3) after 15–24 weeks (table 3, figure 1). After two doses, protection against delta increased to 91·8% (91·2–92·3) after 2–14 weeks but was 71·9% (67·9–75·4) after 25–29 weeks. A third dose increased protection against delta to 96·0% (92·2–97·9) after 2–14 weeks; further follow-up was limited by the emergence of the omicron variant.

In adolescents with previous infection and at least one vaccine dose, protection against symptomatic delta infection was greater than 90% with limited waning over time after vaccination, irrespective of the infecting strain (wildtype, alpha, or delta) or whether the previous infection occurred before or after vaccination (table 3, figure 2).

Overall, mRNA vaccination protected against symptomatic omicron infection in adolescents with no previous infection and provided additional protection in adolescents with previous infection, but to a lower extent than against delta (figure 1, table 4). In adolescents with no previous infection, protection against omicron was 18·8% (95% CI 17·2–20·3) at 2–14 weeks after vaccine dose one and peaked at 64·5% (63·6–65·4) at 2–14 weeks after dose two, before declining to 19·4% (11·7–26·4) by

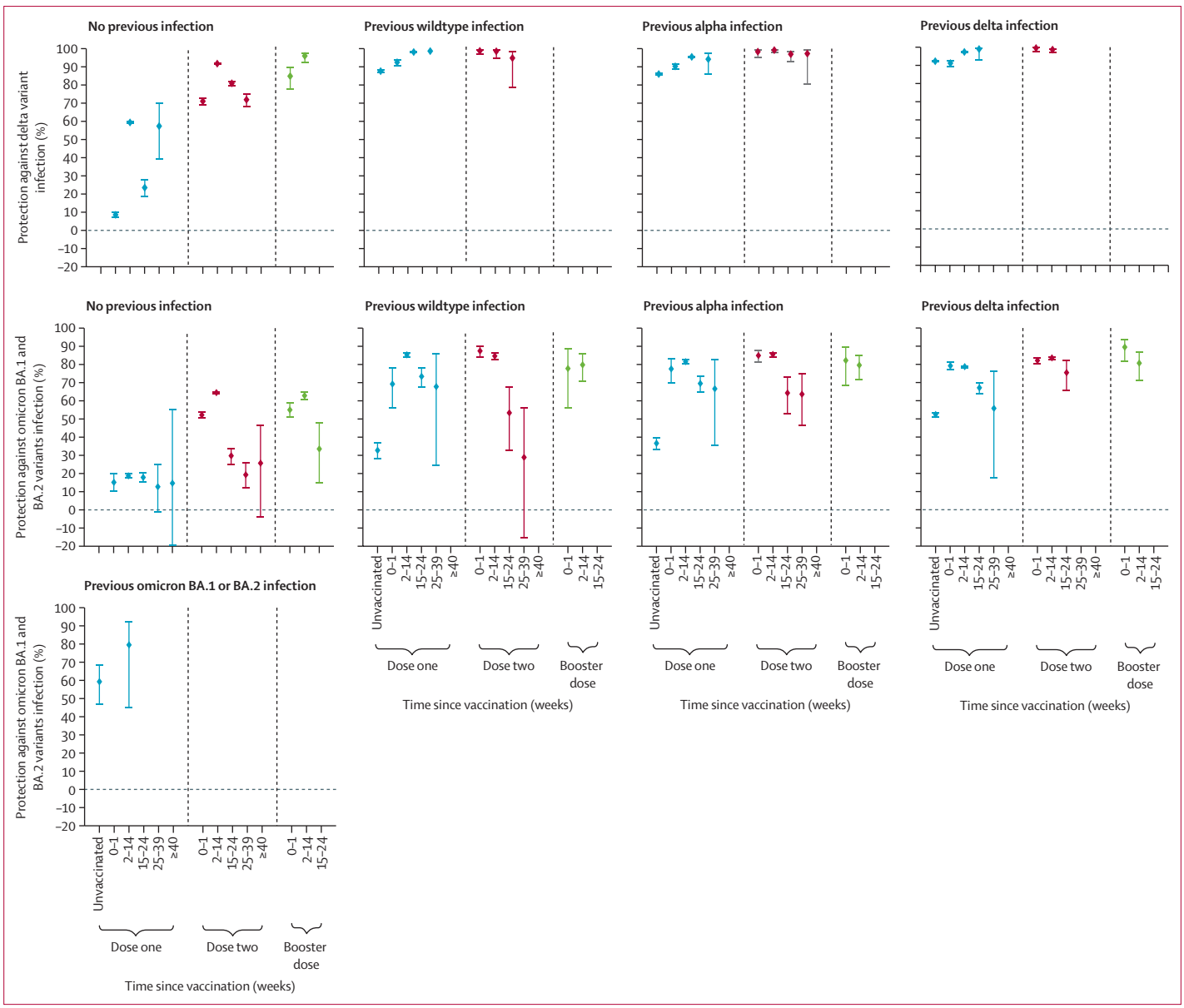

Figure 1: **Protection from combinations of vaccination and previous infection with wildtype, alpha, delta, and omicron variants BA.1 and BA.2 of SARS-CoV-2 against delta and omicron BA.1 and BA.2 infection, by time since vaccination**
Error bars show 95% CIs.

25–39 weeks after dose two (figure 1, table 4). Protection increased to 62·9% (95% CI 60·5–65·1) at 2–14 weeks after dose three and then declined.

Vaccination in adolescents who had previous infection with wildtype, alpha, delta, or omicron variants increased protection against symptomatic omicron infection, with higher peaks than in adolescents with no previous infection, reaching 85·3% (95% CI 83·7–86·8) with previous wildtype infection, 81·5% (80·0–82·9) with alpha, 78·8% (77·9–79·5) with delta, and 79·6% (44·9–92·4) with omicron, at 2–14 weeks after one vaccine dose (figure 1, table 4).

Protection against omicron infection waned after the first vaccine dose and then increased to 80–90% at 2–14 weeks after the second dose before waning again, to a greater extent in adolescents with previous wildtype infection (reaching a nadir of 53·4%, 95% CI 32·7–67·7), albeit with wide CIs, than in those with previous alpha infection (63·6%, 46·0–75·5) or previous delta infection (75·5%, 65·6–82·5), at 15–24 weeks after dose two (figure 1, table 4). A third vaccine dose boosted protection against omicron infection to 80–90% in adolescents who had previous infection with wildtype, alpha, or delta, but follow-up was limited to 2–14 weeks after dose three (table 4).

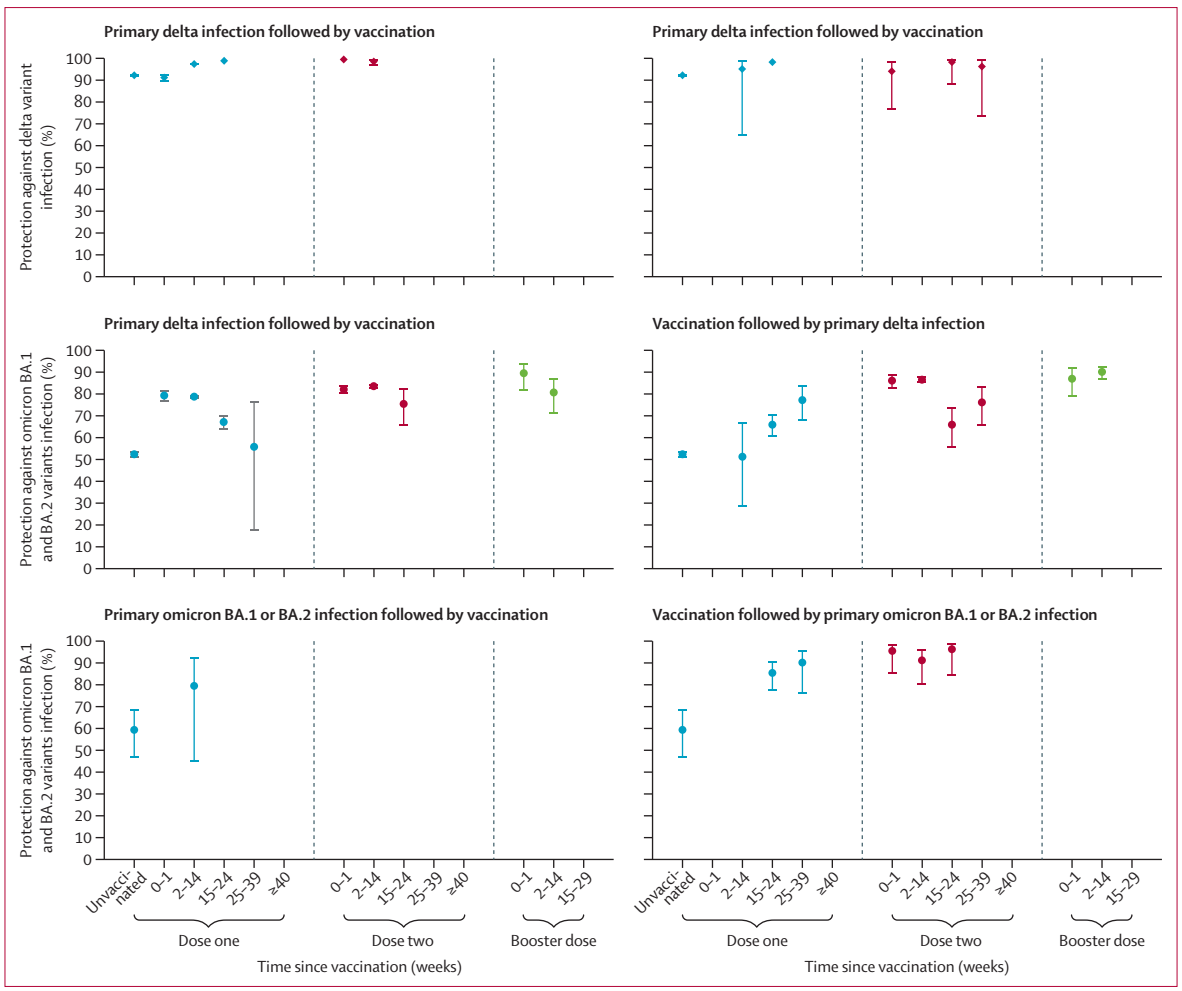

Figure 2: **Protection from combinations of primary SARS-CoV-2 infection followed by vaccination or vaccination followed by primary SARS-CoV-2 infection with delta or omicron BA.1 and BA.2 variants against delta or omicron BA.1 and BA.2 reinfection, by time since vaccination**
Error bars show 95% CIs.

Similar trends in protection against symptomatic omicron infection were observed for adolescents who had previous infection with delta before vaccination compared with those who had previous delta infection after vaccination (figure 2, table 4).

There was short follow-up for adolescents vaccinated after previous omicron infection, with wide CIs because of small case numbers (figure 1, table 4). Adolescents who were vaccinated before primary omicron infection showed the highest protection against symptomatic omicron reinfection, with protection remaining high at 90·2% (95% CI 75·9–96·0) at 25–39 weeks after dose one and 96·4% (84·4–99·1) at 15–24 weeks after dose two (figure 2, table 4).

Discussion

There are limited data on the effects of natural and vaccine-induced immunity against SARS-CoV-2 in adolescents, with most reported studies focusing on adults. We found that primary SARS-CoV-2 infection with wildtype (estimated protection of 87·6%), alpha (86·1%), or delta (92·3%) was highly protective against subsequent symptomatic delta infection in unvaccinated adolescents, but less so against symptomatic omicron infection (32·7% with wildtype, 36·6% with alpha, and 52·4% with delta), while previous omicron infection provided an estimated protection of 59·3% against omicron reinfection. In adolescents with no previous infection, two mRNA vaccine doses provided an estimated protection of 92·3% against delta and although protection waned with time, high protection was restored after a third dose. By contrast, two doses provided lower protection (64·5%) against symptomatic omicron infection, with waning protection after each dose. In adolescents with previous infection, vaccination with one or two doses provided high protection against delta irrespective of the SARS-CoV-2 variant responsible for primary infection, which was sustained after each vaccine dose, with very little waning. Vaccination also added protection against symptomatic omicron infection in

	No previous infection	Previous wildtype infection before vaccination	Previous alpha infection before vaccination	Previous delta infection before vaccination	Previous omicron infection before vaccination	Previous delta infection after vaccination	Previous omicron infection after vaccination
Unvaccinated	..	32·7% (27·7 to 37·4)	36·6% (32·9 to 40·1)	52·4% (50·9 to 53·8)	59·3% (46·7 to 69·0)	52·4% (50·9 to 53·8)	59·3% (46·7 to 69·0)
Dose one, Pfizer							
0–1 week	15·2% (9·9 to 20·1)	69·2% (55·9 to 78·5)	77·6% (69·5 to 83·6)	79·3% (76·7 to 81·6)	..	..	..
2–14 weeks	18·8% (17·2 to 20·3)	85·3% (83·7 to 86·8)	81·5% (80·0 to 82·9)	78·8% (77·9 to 79·5)	79·6% (44·9 to 92·4)	51·2% (28·4 to 66·8)	..
15–24 weeks	17·9% (14·9 to 20·7)	73·4% (67·2 to 78·4)	69·5% (64·5 to 73·8)	67·2% (63·7 to 70·3)	..	65·9% (60·5 to 70·6)	85·5% (77·5 to 90·6)
25–39 weeks	12·8% (–1·6 to 25·1)	67·8% (24·1 to 86·3)	66·7% (35·2 to 82·9)	55·8% (17·2 to 76·4)	..	77·2% (67·5 to 84)	90·2% (75·9 to 96·0)
≥40 weeks	14·7% (–19·9 to 55·4)	..	..	..	..	..	..
Dose two, Pfizer							
0–1 week	52·2% (50·4 to 53·9)	87·4% (83·5 to 90·4)	84·9% (81·3 to 87·8)	82·1% (80·1 to 83·9)	..	86·1% (82·3 to 89·1)	95·5% (85·3 to 98·6)
2–14 weeks	64·5% (63·6 to 65·4)	84·7% (82·6 to 86·5)	85·5% (84·0 to 86·9)	83·5% (82·5 to 84·5)	..	86·5% (85·1 to 87·8)	91·2% (80·0 to 96·1)
15–24 weeks	29·8% (24·9 to 34·2)	53·4% (32·7 to 67·7)	64·3% (52·4 to 73·3)	75·5% (65·6 to 82·5)	..	65·9% (55·2 to 74·1)	96·4% (84·4 to 99·1)
25–39 weeks	19·4% (11·7 to 26·4)	28·9% (–15·5 to 56·3)	63·6% (46·0 to 75·5)	..	..	76·1% (65·3 to 83·6)	..
≥40 weeks	25·7% (–4·2 to 47·0)	..	..	..	..	..	..
Booster dose, any mRNA vaccine							
0–1 week	55·1% (50·7 to 59·1)	77·7% (55·7 to 88·8)	82·2% (68·1 to 90·1)	89·5% (81·7 to 94·0)	..	87·0% (78·8 to 92·0)	..
2–14 weeks	62·9% (60·5 to 65·1)	79·8% (70·4 to 86·3)	79·6% (71·4 to 85·5)	80·7% (71·1 to 87·1)	..	90·1% (86·6 to 92·7)	..
15–24 weeks	33·6% (14·6 to 48·3)	..	..	..	..	..	..

Data are point estimate (95% CI).

Table 4: **Protection from combinations of vaccination and previous infection with wildtype, alpha, delta, and omicron BA.1 and BA.2 variants of SARS-CoV-2 against omicron BA.1 and BA.2 variant infection by time since vaccination**

adolescents with previous infection, but with a lower peak and greater waning after each vaccine dose. High protection was observed against symptomatic omicron reinfection in vaccinated adolescents who had previous infection with omicron.

Our results support the findings of studies in adults that have shown high protection from previous infection against reinfection with pre-omicron variants.[15,21] A study in Qatar reported that previous infection was associated with 90·2% protection (95% CI 81·9–94·6) against delta reinfection and 61·9% (48·2–72·0) against omicron in unvaccinated adults.[21] This is consistent with our data in unvaccinated adolescents showing lower protection against reinfection with omicron than with delta, which was likely to be because omicron variants harbour mutations that lead to evasion of natural and vaccine-induced immunity.[22] Reassuringly, studies in adults have shown similar protection from mRNA vaccines against both BA.1 and BA.2 subvariants.[20]

As previously shown in adults,[13,23] we found limited, short-term protection from vaccination against symptomatic omicron infection, especially when compared with protection against delta in adolescents with no previous infection. We have previously reported higher protection in adolescents aged 12–15 years and those aged 16–17 years against symptomatic delta infection than against symptomatic omicron infection, including rapid waning in protection against symptomatic omicron infection after each vaccine dose in those aged 16–17 years.[13] In this study, we found that protection against symptomatic omicron infection wanes rapidly after each vaccine dose in adolescents with no previous infection and remained low at an estimated 33·6% even after three vaccine doses (at 15–24 weeks after vaccination). In a study in adults in Qatar, there was no protection against omicron BA.2 infection from 6 months after two BNT162b2 vaccine doses and 52·2% (95% CI 48·1–55·9) protection at 43 days after three doses.[16] Although timepoints are not directly comparable, consistent with data from the study in Qatar, we also observed a substantial reduction in protection against omicron infection to 19·4% at 25–39 weeks after dose two and 62·9% at 2–14 weeks after dose three.

Consistent with emerging literature in adults,[15,16,21] and laboratory data in children and adolescents,[24] we found that hybrid immunity provided the most robust protection against SARS-CoV-2 infection. In this study, protection against delta variant infection remained higher than 90% after previous infection with any pre-omicron variant and one or two BNT162b2 vaccine doses. Although vaccination improved protection against omicron in adolescents with previous infection, peak protection remained lower than against delta, with substantial waning over time after the first and second vaccine dose, although protection remained at 80–90% up to 3 months after the third dose. These data are consistent with the study in Qatar where a combination of previous infection and two BNT162b2 vaccine doses was associated with protection against BA.2 infection of 55·1% (95% CI 50·9–58·9) at a median of 270 days (IQR 213–296) between the second dose and PCR test, and a combination of previous infection and

three BNT162b2 doses was associated with protection of 77·3% (95% CI 72·4–81·4) at a median of 43 days (IQR 26–65) between the third dose and PCR test.[16] These findings are consistent with laboratory studies that have shown that hybrid immunity provides broader protection, with higher neutralising antibody activity, against SARS-CoV-2 than previous infection or vaccination alone.[25]

Waning of SARS-CoV-2 antibodies has been well documented after natural infection and vaccination. Indeed, antibody waning is considered the main reason for recurrent infections with seasonal coronaviruses.[26] We also observed rapid waning of immunity against infection offered by vaccination in adolescents with no previous infection, consistent with adult studies.[15,27] Among adolescents with previous infection, we found large disparities with delta and omicron, with high protection against symptomatic delta infection maintained even after one vaccine dose. By contrast, vaccination in adolescents with previous infection was associated with lower peak protection against symptomatic omicron infection and greater waning of protection after each vaccine dose compared with protection against delta. Notably, though, vaccination plus primary omicron infection provided the most robust protection against omicron reinfection, although we were unable to assess duration of protection because of short follow-up duration. As with delta infection, omicron infection followed by vaccination would be likely to also provide robust protection, but we did not have sufficient data to assess this in our cohort. The sequence of infection and vaccination is likely to be of little importance, with protection against reinfection following primary infection then vaccination being similar to vaccination then primary infection, especially against delta but also against omicron.[15]

Our population-based analysis of protection against symptomatic infection after infection-induced, vaccine-induced, and hybrid immunity in adolescents is consistent with adult studies. With the high case rates observed with omicron globally, and the emergence of multiple immune-evasive omicron subvariants, as in England,[28] nearly all children are likely to have been exposed to and developed some immunity to SARS-CoV-2. Additionally, adolescents in many countries have been vaccinated against COVID-19, providing them with additional protection.

Since community testing ended in England, new subvariants of omicron, BA.4 and BA.5, have emerged and appear to be more evasive than previous omicron subvariants, resulting in high rates of reinfections irrespective of previous infection or vaccination status, although COVID-19-related hospitalisations and deaths in adults remain low.[29] Taken together, these data question the need for COVID-19 vaccine booster doses in populations with already high immunity and low risk of severe disease; however, waning immunity will need to be further examined, with regard to additional follow-up duration, evolving variants, and updated vaccines.

Free community PCR or lateral flow tests ended in the UK in March, 2022, and, therefore, analyses such as this will no longer be possible and will be restricted to monitoring severe outcomes, such as hospitalisation and death.

The large scale of testing and sequencing in the UK, and the use of the national vaccination register, has allowed broad evaluation of protection in adolescents against delta and omicron, as well as evaluation of protection from previous infection and hybrid immunity. Our analysis, however, has some limitations. When assessing previous infection, the last infection episode was used; it is therefore possible that some individuals might have had earlier first infections that were not considered, although numbers were likely to be small because testing was so widely available, and this was unlikely to affect the overall results. Booster doses were given to adolescents during the omicron wave, which prevented longer-term follow-up of protection against the delta variant. Because most adolescents were vaccinated before omicron began circulating, we were unable to assess protection beyond 2–14 weeks after one vaccine dose for this cohort. Some misclassifications might have occurred due to imperfect sensitivity and specificity of PCR testing, and the use of S target-negative status to identify variants. It is possible, due to using real-world data, that differences not adjusted for in our multivariable analysis might be present between groups compared, as well as differences in behaviours in those who were tested versus those who chose not to test when unwell. However, we expect these potential differences to be small and similar across the groups compared in this analysis. Estimates of protective effects of previous infections are likely to be underestimated due to missing infections where testing was not done; however, this bias will affect any design where regular asymptomatic testing or antibody testing is not done. Our analysis did not assess protection against severe disease, hospitalisation, or death. Previously we and others have shown that vaccination offers high protection against hospitalisation in adolescents with no previous infection.[13,14] Using hospitalisations as a marker of severe COVID-19 will also be difficult because of disproportionately higher hospitalisation rates among people with underlying comorbidities compared with healthy adolescents, and high rates of incidental infections among people who are hospitalised during periods of high community infection rates.[30]

Previous infection with any SARS-CoV-2 variant provides some protection against reinfection, even against omicron but more so against delta. mRNA COVID-19 vaccination always adds to protection, irrespective of previous infection. Vaccination and previous infection together provide very high protection against delta, with little waning over time. Vaccination

alone provides low-to-moderate protection against omicron, with waning protection after each dose, whereas hybrid immunity provides the most robust protection against both omicron and delta. Following high infection rates due to omicron subvariants, our findings question the need for additional vaccine doses in adolescents; however, waning and emerging variants must be taken into account in the future. We have shown that additional vaccine doses provide low-to-moderate added protection for a limited period against omicron. Further studies are needed to assess the risk of post-COVID-19 symptoms after recurrent infection and infection with new variants in vaccinated and unvaccinated children and adolescents.

Contributors

NA and SNL were responsible for study conceptualisation. NA, JS, and FK were responsible for methodology, validation, investigation, resources, and data curation. NA was responsible for the formal analysis. AAP, SNL, and NA were responsible for visualisation. NA and AAP directly accessed and verified the underlying data reported in the manuscript. AAP was responsible for writing the original draft with NA and SNL. All authors were involved in writing, reviewing, and editing, and MER, JL-B, SNL, and NA were responsible for supervision. All authors had full access to the data in this study and read and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Applications for relevant anonymised data should be submitted to the UK Health Security Agency office for Data Release at https://www.gov.uk/government/publications/accessing-ukhsa-protected-data.

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