Effectiveness of BNT162b2 vaccine against SARS-CoV-2 Delta and Omicron infection in adolescents, Norway, August 2021 to January 2022

Supplementary appendix

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1. Data sources and linkages

All data in this study came from the national emergency preparedness register, Beredt C19 [1]. Beredt C19 contains individual-level data from central health registries, national clinical registries and other national administrative registries. The data sources and variables used are shown in Table S1

Table S1. Data sources in the Norwegian preparedness registry (BeredtC19) used in this study and variables retrieved from each source

Norwegian Abbreviation	Full name of data source	Information obtained
DSF	The National Population Register	Age, Sex, County of residence*, Country of birth, Date of death
SYSVAK	The National Immunisation Register	Date of vaccination, Vaccine product type
NIPaR	Norwegian Intensive Care and Pandemic Registry	Date of hospitalisation, COVID-19 as main cause of admission, Date of ICU admission
MSIS	The Surveillance System for Infectious Diseases	Date of sample of SARS-CoV-2 positive test, Date of COVID-19 associated death
SSB	Statistics Norway	"living crowded" (see definition below)
Beredt C19 risikogrupper	Table prepared in BeredtC19 Source: Norwegian Patient Registry (NPR): individual level data from all public specialist health-care services in Norway.	Defines risk groups (see definition below)

** The county of residence was updated in January 2022, which might lead to some errors for individuals who have moved the last half year*

Reported cases of COVID-19, reinfections and deaths: We included data on reported cases of laboratory-confirmed SARS-CoV-2 infection and deaths from the Norwegian Surveillance System for Communicable Diseases (MSIS). As of January 2022, in MSIS, reinfections are registered if there are ≥6 months between two positive sampling dates for an individual, although this will exclude reinfections within a 6-month period, of which the Omicron variant could be of higher risk.

Laboratory testing for variants: Data on virus variants came from the MSIS laboratory database (national laboratory database), which receives SARS-CoV-2 test results from all Norwegian microbiology laboratories [2].

Additional definitions used:

Crowding: Individuals are considered to live in crowded conditions if the number of rooms is lower than the number of residents or one resident lives in one room, and the number of square metres (P-area) is below 25 sq. m. per person. If the number of rooms or the P-area is not specified, a household will be regarded as crowded if one of these criteria is met [3].

Risk groups: Some underlying medical conditions increase the risk of severe COVID-19 outcomes, regardless of age. These individuals have been prioritised in the vaccination campaigns in Norway. The underlying comorbidities that have been defined as increasing the risk of severe COVID-19 are divided into two groups:

High risk: people with diseases/conditions that carry a high risk of severe COVID-19:

- Organ transplant
- Immunodeficiency
- Haematological cancer in the last five years
- Other active cancers
- Neurological or neuromuscular diseases that cause impaired cough or lung function (e.g., ALS and cerebral palsy)
- Chronic kidney disease, or significant renal impairment.

Medium risk: people with diseases/conditions that entail a moderate risk of severe COVID-19:

- Chronic liver disease or significant hepatic impairment
- Diseases requiring immunosuppressive therapy
- Diabetes
- Chronic lung disease including cystic fibrosis and severe asthma which have required the use of high dose inhaled or oral steroids within the past year
- Obesity with a body mass index (BMI) of ≥35 kg/m2
- Dementia
- Chronic heart and vascular disease (with the exception of high blood pressure) and stroke

2. Vaccine effectiveness: Statistical analyses, including sensitivity analyses.

We estimated the vaccine effectiveness against all infections (Delta- and Omicron infections in separate analyses), using Cox proportional hazards models with vaccination status as a time-dependent covariate, and with explicit time to account for changes in the baseline hazard over time. Vaccine status is implemented as a regular parameter and assumes proportionality with vaccine effectiveness defined as $100*(1-\beta)$, with β the proportional hazard associated with vaccine status. Stratified Cox models are a useful extension of the standard cox models to allow for covariates with no-proportional hazards. Using stratification to adjust for the covariates allow each combination of covariate groups to have their own baseline hazard rate, while still assuming that vaccination leads to a proportional change in risk of infection. In all our adjusted vaccine effectiveness estimates presented here, we stratified for sex, country of birth, county of residence, crowding and underlying comorbidities associated with increased risk of severe COVID-19. The advantage of using a stratified model to control for confounders is that it does so based on fewer assumptions than standard regression models, that can introduce bias due to model misspecification etc. A drawback is that stratifying unnecessarily (even though the PH assumption is met) reduces estimation efficiency, although the loss is typically very small. In our analysis we did not add tests for proportionality for all covariates. This is not an issue in our results since we used stratified Cox and we stress the results that are statistically significant (meaning with enough power). The STATA code used for the stratified Cox analyses was *"stcox i,vaccine_status, strata (sex country_of_birth county_of_residence household_crowding underlying_comorbidities)"*.

More specifically, we estimated the vaccine effectiveness among individuals with no prior SARS-CoV-2 infection after receiving one dose for individuals 12-15 years old and after one or two doses for individuals 16-17 years old against a) all reported infections from 25 August to 25 November, b) reported Delta infections from 25 August 2021 to 16 January 2022 and c) reported Omicron infections from 26 November to 16 January. The analyses for all reported cases during the period 25 August to 25 November is conducted assuming that all reported cases were Delta since Delta accounted for nearly 100 % of all samples analysed for genetic variant in that period. We restricted the vaccine effectiveness analyses for Omicron infection after the first case of Omicron was reported in adults on the 26 of November 2021. We closed the follow up period on 16 January since the comprehensive screening activity ceased as Omicron reached more than 90% prevalence.

In the Cox proportional hazards models used, unvaccinated person-time included days before receiving the first dose of a COVID-19 vaccine (if received) and vaccinated person-time included number of days following the receipt of one or two doses of the vaccine (based on the vaccination programme). For adolescents that got infected, the end/event time for these analyses was the first sampling date where the participants tested positive (right censored). We also right-censored individuals at the time of death (all cause), date of third dose or end of follow-up period (25 of November or 16 of January according to the last day for the three outcomes).

Below, in table S2, we present the results included in the main article from our adjusted vaccine effectiveness analyses. In addition, we present the results from the sensitivity analyses that were performed in table S3 to evaluate the impact in estimating vaccine effectiveness for a specific variant when only including (using data) on screened cases since usually only part of all reported cases is screened for variant.

Table S2: Adjusted vaccine effectiveness (aVE) for age 12-15 years (orange) and 16-17 (blue) by vaccination status against a) all reported infections from 25 August to 25 November, b) reported Delta infections from 25 August 2021 to 16 January 2022, and c) reported Omicron infections from 26 November to 16 January. We estimated aVE using Cox regression stratified by age, sex, county of residence, country of birth, crowding and underlying comorbidities.

	Age group 12-15		Age group 16-17	
	Number of cases	**Adjusted vaccine effectiveness (95% CI)**	**Number of cases**	**Adjusted vaccine effectiveness (95% CI)**
a) All infections, 25 August to 25 November 2021				
Unvaccinated	9,800	Ref	4,739	Ref
1st dose, 0-20 days	1,506	16·8 (11·12–22·0)	2,075	21·4 (16·4–26·0)
1st dose, 21-48 days	952	65·0 (62·3–67·6)	517	61·5 (57·1–65·5)
1st dose, 49-76 days	1,601	57·3 (54·4–60·0)	1,305	48·0 (43·3–52·4)
1st dose, ≥77 days	11	70·2 (45·9–83·6)	279	47·5 (39·0–54·9)
2nd dose, 0-6 days	NA	NA	78	66·7 (57·9–73·7
2nd dose, 7-34 days	NA	NA	45	90·7 (87·4–93·1)
2nd dose, 35-62 days	NA	NA	6	92·3 (82·9–96·6)
2nd dose, ≥63 days	NA	NA	13	87·8 (78·8–92·9)
b) Delta infections, 25 August 2021 to 16 January 2022				
Unvaccinated	6,783	Ref	2,771	Ref
1st dose, 0-20 days	665	32·3 (25·9–38·2)	929	23·4 (16·3–29·8)
1st dose, 21-48 days	379	67·9 (64·0–71·4)	246	62·6 (56·2–68·0)
1st dose, 49-76 days	1,257	55·8 (52·7–58·8)	461	47·3 (40·0–53·8)
1st dose, ≥77 days	2,640	48·8 (46·0–51·5)	515	29·3 (20·4–37·1)
2nd dose, 0-6 days	NA	NA	216	51·4 (43·2–58·5)
2nd dose, 7-34 days	NA	NA	164	90·8 (89·1–92·3)
2nd dose, 35-62 days	NA	NA	34	92·8 (89·8–94·9)
2nd dose, ≥63 days	NA	NA	29	83·7 (75·9–89·0)
c) Omicron infections, 26 November 2021 to 16 January 2022				
Unvaccinated	973	Ref	214	Ref
1st dose, 0-20 days	49	21·2 (-5·1–53·8)	11	15·1 (-56–53·8)
1st dose, 21-48 days	108	16·2 (-2·4–31·3)	39	-33·7 (-88·3–5·1)
1st dose, 49-76 days	125	-1·3 (-22·4–16·2)	19	-16·8 (-87·3–27·1)
1st dose, ≥77 days	2,779	-12·8 (-21·7– -4·6)	110	-5·3 (-32·9–16·6)
2nd dose, 0-6 days	NA	NA	15	9·5 (-55·2–47·3)
2nd dose, 7-34 days	NA	NA	204	53·1 (42·6–61·7)

2nd dose, 35-62 days	NA	NA	330	45·7 (34·8–54·7)
2nd dose, ≥63 days	NA	NA	114	23·3 (2·7–39·5)

Note 1: The Vaccine effectiveness in 0-6 days after the second dose probably reflects the effect of the first vaccine dose.

Note 2: Overall, during 26 November 2021 to 16 January 2022: There were 8,013 Delta infections reported, of which 8011 were included in the Cox regression (two cases had date of event before date of entry due to errors). From those 8,011 Delta cases, the 6,507 were in age group 12-15 and 1,504 in the age group 16-17 years. Moreover, there were 5,123 Omicron infections of which 5,120 were included in the Cox regression (three cases had date of event before date of entry due to errors). From those 5,120 Omicron cases, the 4,064 were in age group 12-15 and 1,056 in the age group 16-17.

Table S3: Adjusted vaccine effectiveness (aVE) by age group and vaccination status against a) all reported infections from 25 August to 25 November and b) reported Delta infections from 25 August to 25 November2021. We estimated aVE using Cox regression stratified by age, sex, county of residence, country of birth, crowding and underlying comorbidities.

	Age group 12-15		Age group 16-17	
	Number of cases	Adjusted vaccine effectiveness (95% CI)	Number of cases	Adjusted vaccine effectiveness (95% CI)
a) All infections				
Unvaccinated	9,800	Ref	4,739	Ref
1st dose, 0-20 days	1,506	16·8 (11·12–22·0)	2,075	21·4 (16·4–26·0)
1st dose, 21-48 days	952	65·0 (62·3–67·6)	517	61·5 (57·1–65·5)
1st dose, 49-76 days	1,601	57·3 (54·4–60·0)	1,305	48·0 (43·3–52·4)
1st dose, ≥77 days	11	70·2 (45·9–83·6)	279	47·5 (39·0–54·9)
2nd dose, 0-6 days	NA	NA	78	66·7 (57·9–73·7
2nd dose, 7-34 days	NA	NA	45	90·7 (87·4–93·1)
2nd dose, 35-62 days	NA	NA	6	92·3 (82·9–96·6)
2nd dose, ≥63 days	NA	NA	13	87·8 (78·8–92·9)
b) Delta variant				
Unvaccinated	3,945	Ref	2,233	Ref
1st dose, 0-20 days	530	27·5 (19·1–35·0)	889	23·6 (16·3–30·3)
1st dose, 21-48 days	285	68·9 (64·3–72·9)	227	63·3 (56·5–69·0)
1st dose, 49-76 days	463	56·0 (50·3–61·0)	398	49·4 (41·0–56·7)
1st dose, ≥77 days	3	70·1 (6·2–90·5)	68	46·5 (27·8–60·3)
2nd dose, 0-6 days	NA	NA	24	62·5 (42·9–75·4)
2nd dose, 7-34 days	NA	NA	14	89·9 (82·8–94·1)
2nd dose, 35-62 days	NA	NA	0	–
2nd dose, ≥63 days	NA	NA	8	80·3 (60·0–90·3)

Note: Overall, during 25 August 2021 to 25 November 2021: There were 22,937 all infections of which 22,935 were included in the Cox regression (two cases had date of event before date of entry due to errors). From those 22,935 all infections, the 13,878 were in age group 12-15 and 9,057 in the age group 16-17. There were 9,092 Delta infections reported, of which 9,090 were included in the Cox regression (two cases had date of event before date of entry due to errors). From those 9,090 Delta cases, the 5,229 were in age group 12 -15 and 3,861 in the age group 16-17 years.

3. References

1. Norwegian Institute of Public Health. Emergency preparedness register for COVID-19 (Beredt C19). Oslo: Norwegian Institute of Public Health; 2021 [cited 2022 Mar 10]. Available from: https://www.fhi.no/en/id/infectious-diseases/coronavirus/emergency-preparedness-register-for-covid-19/.
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