The effectiveness of BNT162b2 mRNA vaccine against COVID-19 caused by Delta variant of SARS-CoV-2: a systematic review and meta-analysis

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Abstract
Meta-analyses were utilized to determine the overall effectiveness of BNT162b2 mRNA vaccine (Pfizer vaccine) against COVID-19 caused by Delta variant from large real-world studies. A systematic literature search with no language restriction was performed in electronic databases to identify eligible observational studies that reported the effectiveness of the BNT162b2 mRNA vaccine to prevent reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 caused by Delta variant of SARS-CoV-2 (B.1.617.2). Random-effects meta-analysis model was used to estimate the pooled odds ratio (OR) at a 95% confidence interval, and the vaccine effectiveness was indicated as (pooled OR – 1)/OR. Seven studies were included for this meta-analysis. The meta-analysis revealed that the administration of BNT162b2 mRNA vaccine protected against RT-PCR confirmed COVID-19 caused by Delta variant ≥ 21 days after the first dose, with vaccine effectiveness of 55% (95% confidence interval 46–63%), as well as ≥ 14 days after the second dose, with vaccine effectiveness of 81% (95% confidence interval 69–88%). In conclusion, the BNT162b2 mRNA vaccine offers a substantial protection rate against RT-PCR confirmed COVID-19 caused by the Delta variant upon full vaccination, albeit with slightly reduced effectiveness relative to other strains of SARS-CoV-2.

Keywords BNT162b2 · COVID-19 · Delta · Vaccine · Variant

Introduction
The Delta variant of SARS-CoV-2, also known as B.1.617.2, belongs to a viral lineage of SARS-CoV-2 first identified in India during an intense wave of coronavirus disease 2019 (COVID-19) in April and May 2021. The Delta variant is highly transmissible, where it was reported that it could be more than twice as transmissible as the original strain of SARS-CoV-2 (Andrews et al. 2021). COVID-19 caused by Delta variant still lead to typical symptoms including headache, sore throat, runny nose, and fever, but cough and loss of smell are less common. The lineage has since proliferated and linked to a resurgence of COVID-19 cases in many parts of the world, including those with robust vaccination drives, and this may lead to phenomenon of hyperlocal outbreaks (concentrated amounts of cases in neighborhoods with low vaccination rate) which could overwhelm the healthcare
system due to unequal proportion of vaccination across different areas (Blanquart et al. 2021). Therefore, there have been concerns in the medical fraternity that the currently available COVID-19 vaccines may not be adequate to protect against COVID-19 caused by the Delta variant (Bian et al. 2021). This paper aimed to summarize through meta-analyses the overall effectiveness of the BNT162b2 mRNA vaccine against COVID-19 caused by Delta variant from real-world studies.

Methods

This study was conducted and reported according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). Two investigators (CSK and SSH) independently conducted systematic literature search in several electronic databases, including PubMed, Google Scholar, Scopus, Web of Science, and medRxiv, in September 2021. The search strategy was designed to identify all publications which reported the effectiveness of the BNT162b2 mRNA vaccine to prevent reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 caused by Delta variant of SARS-CoV-2 (B.1.617.2). We applied various combinations of Boolean operators for the following keywords during our search: [(SARS-Cov-2 OR 2019-nCOv OR COVID-19 OR coronavirus) AND (vaccine or vaccination) AND (variant)]. In addition, the references from narrative reviews or other systematic reviews were cross-checked to identify additional missing publications during the initial search.

Studies were eligible for inclusion in our systematic review and meta-analysis if they (1) were observational studies (of any design, for example, case–control, cohort, case series); (2) reported the effectiveness of the BNT162b2 mRNA vaccine to prevent reverse transcription-polymerase chain reaction (RT-PCR) confirmed COVID-19 caused by Delta variant of SARS-CoV-2 (B.1.617.2); (3) compared vaccine effectiveness between vaccinated and unvaccinated individuals or between pre- and post-vaccination; and (4) reported adjusted effectiveness estimates. For two or more studies that utilized the same data source for their investigations on vaccine effectiveness, we included the study that performed analysis with the latest data cut-off date. Studies that utilized surrogate measures of vaccine effectiveness against COVID-19 caused by Delta variant of SARS-CoV-2 by reporting vaccine effectiveness during Delta predominance period were excluded. Studies that reported unadjusted effectiveness estimates, and studies that reported the effectiveness of the vaccine to prevent COVID-19-related mortality or COVID-19-related hospitalization were also excluded. We did not include preprints editorials, commentaries, and narrative reviews.

The outcome of interest, namely vaccine effectiveness, was defined as a relative risk reduction in RT-PCR confirmed COVID-19 caused by Delta variant in vaccinated individuals (post-vaccination) compared with unvaccinated individuals (pre-vaccination) (Weinberg and Szilagyi 2010). All relevant information from the eligible studies was extracted and recorded in a pre-determined data collection table. The following information was extracted from each included study: first author's surname, year of publication, study design, country where the study was performed, number of participants, the incidence/frequency of COVID-19 in both vaccinated and unvaccinated individuals, adjusted effectiveness estimates, and covariates adjusted in the study. Newcastle–Ottawa Scale was used for critical appraisal of the quality of included observational studies. Two investigators (CSK and SSH) independently evaluated the quality of studies with the Newcastle–Ottawa Scale (Wells et al. 2013) and a Newcastle–Ottawa Scale of at least 8, indicating high quality. Consensus discussions between the two investigators were carried out to resolve disagreements on the inclusion of studies, extraction of study characteristics, and quality appraisal of included studies.

A random-effects model was used to estimate the pooled odds ratio (OR) for the occurrence of COVID-19 caused by Delta variant between vaccinated and unvaccinated individuals, at 95% confidence intervals, when three or more studies were reporting the same type of effect measure (either odds ratio or hazard ratio [HR]). We examined the heterogeneity between studies using the $I^2$ statistics and the $\chi^2$ test, with 50% and $p < 0.10$, respectively, were considered as an indication of the presence of heterogeneity. The vaccine effectiveness was indicated as (pooled HR − 1)/HR or (pooled OR − 1)/OR, together with a 95% confidence interval. All analyses were performed using Meta XL, version 5.3 (Epi-Gear International, Queensland, Australia).

Results and discussion

Our literature search yielded 4441 records. After deduplication and application of eligibility criteria, 14 relevant articles were shortlisted for inclusion through full-text examination (Fig. 1). Of these, eight studies were excluded since they utilized surrogate measures of vaccine effectiveness against COVID-19 caused by Delta variant of SARS-CoV-2 by reporting vaccine effectiveness during Delta predominance period, reporting the effectiveness of vaccines other than vaccines BNT162b2 mRNA vaccine, or reported unadjusted effectiveness estimates. Eventually, seven studies (Andrews et al. 2021; Martínez-Baz et al. 2021; Nasreens et al. 2021;
Sheikh et al. 2021; Skowronski et al. 2021; Tang et al. 2021; Tartof et al. 2021) were included in this systematic review and meta-analysis; all included studies were of retrospective design, with five case-control studies (Andrews et al. 2021; Nasreen et al. 2021; Sheikh et al. 2021; Skowronski et al. 2021; Tang et al. 2021) and two cohort studies (Martínez-Baz et al. 2021; Tartof et al. 2021). The study characteristics are depicted in Table 1. The included studies were originated from Scotland (Sheikh et al. 2021), England (Andrews et al. 2021), Qatar (Tang et al. 2021), Canada (Nasreen et al. 2021; Skowronski et al. 2021) \((n=2)\), Norway (Martínez-Baz et al. 2021), and the United States (Tartof et al. 2021). Age and sex were the most commonly adjusted covariates (adjusted in all included studies). Studies included for meta-analyses (Andrews et al. 2021; Martínez-Baz et al. 2021; Nasreen et al. 2021; Sheikh et al. 2021; Skowronski et al. 2021; Tang et al. 2021) are deemed moderate-to-high quality with a Newcastle–Ottawa Scale ranging from 7 to 8 (Table 1).

The meta-analysis performed using the data extracted from three studies (Martínez-Baz et al. 2021; Nasreen et al. 2021; Tang et al. 2021) revealed a significant protective effect produced by the first dose of BNT162b2 mRNA vaccine (after 14 days or more) against SAR-CoV-2 infection caused by the Delta variant (pooled OR 0.42; 95% confidence interval 0.36–0.49; \(I^2 = 0\%\); \(p = 0.63\); Fig. 2). The pooled estimate shows vaccine effectiveness of 58% (95% confidence interval 51–64%). Similarly, the meta-analysis of two studies (Andrews et al. 2021; Nasreen et al. 2021) revealed a significant protective effect against SAR-CoV-2 infection caused by the Delta variant 21 days post first dose of BNT162b2 mRNA vaccine (pooled OR 0.45; 95% confidence interval 0.37–0.54; \(I^2 = 37\%\); \(p = 0.17\); Fig. 2).
| First author (year), country | Study design | Sample | Total number of participants/specimens | Incidence/frequency of COVID-19 caused by Delta variant of SARS-CoV-2 | NOS |
|-------------------------------|-------------|--------|----------------------------------------|-------------------------------------------------|-----|
|                              |             |        |                                        | Adjusted estimate                                |     |
|                               |             |        | Unvaccinated ≥ 14 days after dose 1    | Unvaccinated ≥ 21 days after dose 1              |     |
|                               |             |        | Adjusted estimate                      | Unvaccinated ≥ 7 days after dose 2               |     |
|                               |             |        |                                        | Adjusted estimate                                |     |
|                               |             |        |                                        | Unvaccinated ≥ 14 days after dose 2              |     |
| Sheikh et al. (2021), Scotland | Retrospective, test-negative, case-control | Scottish population in the EAVE II datasets | 19,543 | n = 3672/117263 (3.1%) | 7 |
|                               |             |        |                                        | n = 163/14214 (1.1%) |     |
|                               |             |        |                                        | OR 0.70 (0.59–0.83) |     |
|                               |             |        |                                        | n = 3672/117263 (3.1%) |     |
|                               |             |        |                                        | n = 208/53679 (0.4%) |     |
|                               |             |        |                                        | OR 0.21 (0.18–0.25) |     |
| Andrews et al. (2021), England | Retrospective, test-negative, case-control | Individuals aged ≥ 16 years who had reported symptoms and were tested for SARS-CoV-2 within 10 days after symptom onset in England | 4,774,735 | OR 0.48 (0.47–0.49) | 8 |
|                               |             |        |                                        | – |     |
|                               |             |        |                                        | – |     |
|                               |             |        |                                        | OR 0.17 (0.16–0.18) |     |

Adjusted covariates include: Age, sex, number of prior COVID-19 tests, date of index case, index of multiple deprivation, and socially disadvantaged neighborhoods.
Table 1 (continued)

| First author (year), country | Study design                  | Sample | Total number of participants/ specimens | Incidence/frequency of COVID-19 caused by Delta variant of SARS-CoV-2 | Adjusted covariates | Adjusted estimate | Unvaccinated ≥ 7 days after dose 2 | Unvaccinated ≥ 14 days after dose 2 | Unvaccinated ≥ 21 days after dose 1 | Unvaccinated ≥ 14 days after dose 1 |
|-----------------------------|--------------------------------|--------|----------------------------------------|-----------------------------------------------------------------------|---------------------|-------------------|-----------------------------------|-------------------------------------|-----------------------------------|------------------------------------|
| Nasreen et al. (2021), Canada | Retrospective, test-negative, case–control | Community-dwelling Ontarians aged 16 years who had symptoms consistent with or a severe outcome attributable to COVID-19, and who were tested for SARS-CoV-2 | 352,531 | \( n = 19,219/89296 \) (21.5%) | \( n = 157/786 \) (20.0%) | OR 0.44 (0.36–0.55) | – | OR 0.39 (0.30–0.49) | – | – | OR 0.13 (0.05–0.36) | – | – | OR 0.15 (0.06–0.41) | Age, sex, public health unit region, period of test, number of SARS-CoV-2 tests in the 3 months prior to 14 December 2020, presence of any comorbidity that increase the risk of severe COVID-19, receipt of 2019/2020 and/or 2020/2021 influenza vaccination, Census dissemination area-level quintiles of household income, proportion of persons employed as non-health essential workers, persons per dwelling, proportion of self-identified visible minorities |
| Tang et al. (2021), Qatar | Retrospective, test-negative, case–control | Resident population of Qatar | 19,823 | \( n = 1254/6134 \) (20.4%) | \( n = 23/204 \) (11.3%) | OR 0.44 (0.28–0.69) | – | – | – | – | – | n=12905995 (21.7%) | n=6333830 (16.4%) | OR 0.56 (0.48–0.63) | Age, sex, nationality, reason for PCR testing, calendar week of COVID-19 test |
| First author (year), country | Study design | Sample | Total number of participants/specimens | Incidence/frequency of COVID-19 caused by Delta variant of SARS-CoV-2 | Adjusted covariates | Adjusted NOS |
|-------------------------------|--------------|--------|----------------------------------------|---------------------------------------------------------------|---------------------|-------------|
| Tartof et al. (2021), US      | Retrospective cohort study | Members in the Kaiser Permanente Southern California (KPSC) health-care system aged ≥ 12 years | 3,436,957 | 83.8 per 100,000 person-years | HR 0.26 (0.15–0.45) | Tartof et al. (2021), US: Age, sex, race/ethnicity, prior PCR positive SARS-CoV-2, prior healthcare utilization, body mass index, comorbidities, Charlson Comorbidity Index, influenza vaccination year prior to index date, pneumococcal vaccination 5 years prior to index date, neighborhood deprivation index. |
| Skowronski et al. (2021), Canada | Retrospective, test-negative, case-control | Individuals aged ≥ 18 years in British Columbia and Quebec, Canada | 1,235,447 | – | – | 8 |
| Martínez-Baz et al. (2021), Norway | Retrospective, test-negative, cohort study | Individuals aged ≥ 18 who were close contacts of COVID-19 cases from April to August 2021 in Navarre, Spain | 30,240 | n = 460/990 (46.5%) | RR 0.37 (0.27–0.49) | Martínez-Baz et al. (2021), Norway: Age, sex, major comorbidities, contact setting (household or other), month and vaccination status of index case. |
with vaccine effectiveness of 55% (95% confidence interval 46–63%).

With the second dose of the BNT162b2 mRNA vaccine, our meta-analysis of six studies (Andrews et al. 2021; Martínez-Baz et al. 2021; Nasreen et al. 2021; Sheikh et al. 2021; Skowronski et al. 2021; Tang et al. 2021) documented an even higher significant protective effect measured at 14 days or more post second dose (pooled OR 0.19; 95% confidence interval 0.12–0.31; $I^2 = 97\%$; $p = 0.01$; Fig. 3), where the pooled estimate shows vaccine effectiveness of 81% (95% confidence interval 69–88%). Thus, there is adequate evidence against our model hypothesis of 'no significant protective effect' against SAR-CoV-2 infection caused by the Delta variant, at the current sample size.

Based on the findings, it appears that the BNT162b2 mRNA vaccine still offers substantial protection against RT-PCR confirmed COVID-19 caused by the Delta variant by 81%. Nevertheless, the protection rate was slightly lower than previously reported in a meta-analysis of real-world studies (Kow et al. 2021) conducted before the Delta predominance period; 55% versus 57% upon partial vaccination and 81% versus 88–96% upon full vaccination.

The reduced effectiveness of the BNT162b2 mRNA vaccine against RT-PCR confirmed COVID-19 caused by the Delta variant relative to other strains of SARS-CoV-2 is most possibly due to the Delta variant notably escapes neutralizing antibodies elicited by vaccination. Previously, in vitro study (Planas et al. 2021) has reported that antibodies elicited by the BNT162b2 mRNA vaccine were efficacious against the Delta variant but about three- to five-fold less potent than they were against the alpha variant (B.1.1.7). It is foreseeable since the BNT162b2 mRNA vaccine encodes an optimized SARS-CoV-2 full-length spike glycoprotein. At the same time, the Delta variant is characterized by the spike glycoprotein mutations T19R, Δ157-158, L452R, T478K, D614G, P681R, and D950N, which contribute to the regulation of spike glycoprotein dynamics (Kannan et al. 2021). Thus, antibodies elicited by the BNT162b2 mRNA
vaccine could have reduced neutralizing effect against the Delta variant.

This systematic review and meta-analysis have its limitations: first, only a small number of studies (7 out of 2258 studies screened) were available for inclusion in this systematic review and meta-analysis, and second, all of the included studies in this systematic review and meta-analysis were of the retrospective design, which can have an inferior level of evidence compared with prospective studies. However, we believe it is of utmost importance to disseminate our findings at this stage to alleviate the concerns of practitioners and the general public surrounding the protection rate of the BNT162b2 mRNA vaccine amid the Delta predominance period. In addition, our findings can offer valuable insights to the policy-makers regarding the urgency to administer booster vaccine doses.

In conclusion, the BNT162b2 mRNA vaccine offers a substantial protection rate against RT-PCR confirmed COVID-19 caused by the Delta variant upon full vaccination, albeit with slightly reduced effectiveness relative to other strains of SARS-CoV-2. Therefore, measures should be taken to hasten the global vaccination efforts to curb COVID-19 transmission, which may drive future emergence of variants of concern, and to perform more investigations on the vaccine adjuvants, which can boost longer-lasting immune response upon vaccination. With our current findings and due to emergence of Omicron variant of SARS-CoV-2, we believe that a booster or a third dose of BNT162b2 mRNA vaccine should be considered, and should prioritize those above 65 years old, 18–64 years old with underlying medical condition, and immunocompromised individuals, who are more prone to severe course of COVID-19.

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