Literature screening report

COVID-19 vaccines and post-vaccination data: Literature update (12)

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Abstract

Currently, the vaccination coverage in Switzerland is around 68.5% of the total population, lagging behind most of its neighbouring countries (e.g., France, Germany, and Italy). By addressing vaccine hesitancy, in addition to setting up non-pharmacological measures and interventions, many countries were more or less successful in alleviating the fifth wave of the COVID-19 pandemic. Scientists suggested that SARS-CoV-2 – the virus that causes COVID-19 – would mutate with time and that vaccination is the key element to fight such variants. Our reports are the outcome of daily COVID-19 vaccine-related literature screenings. This short report addresses the most relevant data on COVID-19 vaccines literature as of 16 December 2021. The current report addresses the latest data on the newly identified variant of concern (VOC) Omicron, vaccine duration of protection, breakthrough infections, and vaccine booster doses.

Content

Preamble

A large number of scientific publications become available on a daily basis, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health plus (SSPH+), upon request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

Background

At the start of 2021, vaccination rollouts demonstrated high vaccine effectiveness against the original SARS-CoV-2 strain; however, concerns about vaccine immunity waning and vaccine effectiveness against variants of concern (VOC), long-term immunogenicity, and viral transmissibility arise.

A study that analysed global vaccine data across 187 countries between 20 December 2020 and 25 April 2021, analysed the correlation between the administration of vaccines and daily COVID-19 cases and deaths. The study concluded that COVID-19 cases and deaths would reduce by **24.43% (95% CI, 18.89-29.59)** and **13.32% (95% CI, 3.81-21.89)** if 10,000 persons become fully vaccinated per day, respectively[1]. However, the study stopped collecting and analysing data in April 2021, a period of mostly Alpha variant predominance, and multiple new variants with mutations able to escape vaccine immunity have emerged since. Given the emergence of VOCs such as the Delta (B.1.617.2) and the recently identified Omicron (B.1.1.529) strain, mutations on the SARS-CoV-2 spike protein partially evade vaccine immunity[2] and the original vaccine-induced herd immunity threshold must be updated[3].

The Omicron strain encompasses several mutations that evade vaccine-induced immunity given that all manufactured vaccines express the ancestral SARS-CoV-2 Spike (S) glycoprotein (the S glycoprotein, in addition to its antigenic domains and epitopes generate neutralizing antibodies against SARS-CoV-2 infection)[4]. As a result, immune responses against the Omicron variant are decreased by when compared to the original wild-type strain[5].

Despite reports of waning vaccine immunity, the latest data continues to demonstrate that COVID-19 vaccines are effective against symptomatic and severe COVID-19 infection,

[1] The effect of the COVID-19 vaccine on daily cases and deaths based on global vaccine data. *Vaccines.* https://www.mdpi.com/2076-393X/9/11/1328/htm

[2] Mutations of SARS-CoV-2 spike protein: Implications on immune evasion and vaccine induced-immunity. *Seminars in Immunology.* https://www.sciencedirect.com/science/article/pii/S1044532321000646?via%3Dihub

[3] The herd immunity threshold must be updated for multi-vaccine strategies and multiple variants. *Scientific Reports.* https://www.nature.com/articles/s41598-021-00083-2

[4] SARS-COV-2 vaccines based on the Spike glycoprotein and implications of new viral variants. *Frontiers in Immunology*. https://www.frontiersin.org/articles/10.3389/fimmu.2021.701501/full

[5] Reduced neutralization of SARS-CoV Omicron B.1.1.529 variant by post-immunization serum. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1

hospitalizations, and deaths. Nevertheless, a third dose of COVID-19 vaccines has demonstrated to boost up the waning immunity and provide a high protection against the illness, hospitalizations, and the more infectious variants, particularly the newly identified Omicron strain. Multiple countries, including Switzerland, have now expanded their vaccination mandate to allow the general population to receive their third booster dose and vaccinate children.

As WHO EUL approved vaccines continue to be administered throughout the world, the scientific community continues to develop and test the efficacy, safety, tolerability, and immunogenicity of numerous COVID-19 vaccine candidates.

This short December report provides an in-depth summary of the latest published data regarding COVID-19 vaccine effectiveness, particularly against the Omicron variant. Our report covers the following questions/points:

Questions addressed

- What do we know so far about the SARS-CoV-2 variant Omicron?
- What are the latest updates regarding vaccine waning immunity and duration of protection?
- What is influencing breakthrough infections?
- What is the latest data on COVID-19 booster doses?

Methodology

The current report screened the databases of PubMed, Embase, medRxiv, bioRxiv, SSRN, Cochrane, and clinical trial databases such as ClinicalTrials and WHO Trial registry for vaccine-related literature as of 16 December 2021. We focused on studies that would help to discuss the points raised above. For more information on the methodology, please refer to previous reports[6].

[6] COVID-19 vaccines: efficacy and safety (Literature Review 1). *Swiss School of Public Health*. https://www.bag.admin.ch/dam/bag/de/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/Literaturrecherchen/literaturrecherchen_covid-19-impfstoffe_20210209.pdf.download.pdf/20210209_Literaturrecherchen_Covid-19-Impfstoffe_EN.pdf

Results and Findings

What do we know so far about the SARS-CoV-2 variant Omicron?

Summary:

On 25 November 2021, a new variant of concern, later named Omicron (B.1.1.529), was firstly reported and detected in South Africa and Botswana. The Omicron variant was identified to contain several mutations on the spike glycoprotein leading to a higher affinity to the ACE-2 domain of the SARS-CoV-2 virus[7,8]. Although not confirmed, this increased affinity could impact the behavior of the virus in terms of its ability to spread, escape existing immunity, and the severity of illnesses it causes. Results estimating the Omicron doubling time have estimated a doubling time ranging from **1.5 to 3 days**[9] with a study estimating **3.38 days** (95% CI, 3.18-3.6) suggesting that the new variant could cause abrupt outbreaks of COVID-19 epidemics[10]. Even though information on the transmissibility and the severity of disease are not yet clear, few studies and preliminary analyses on the effect of the new variant on the efficacy, effectiveness, and immunogenicity of vaccines and booster doses have been released. Based on results examining the effects of the Omicron variant on the immunogenicity induced by the two-dose COVID-19 vaccines, a **11.4 to 84-fold decrease** in mean neutralization titers was reported in comparison to either the wild-type or the Delta variant[11,12,13,14]. By reducing the vaccine-induced immunogenicity of COVID-19 vaccines, the effectiveness of vaccines against symptomatic infection caused by Omicron are expected to be impacted. One study estimated the effectiveness of the BNT162b2 vaccine to be quickly drop to **48.5% (95% CI, 24.3-65.0)** 10-14 weeks

[7] The Omicron variant increases the interaction of SARS-CoV-2 spike glycoprotein with ACE2. *bioRXiv*. https://www.biorxiv.org/content/10.1101/2021.12.06.471377v2

[8] Structural insights of SARS-CoV-2 spike protein from Delta and Omicron variants. *bioRxiv.* https://www.biorxiv.org/content/10.1101/2021.12.08.471777v1

[9] Enhancing Readiness fro Omicron (B.1.1.529) Technical Brief and Priority Actions for Member States. *WHO Technical Document.* https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states

[10] Omicron strain spreads with the doubling time of 3.2-3.6 days in South Africa province of Gauteng that achieved herd immunity to Delta variant. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.12.08.21267494v1.full-text

[11] Reduced neutralization of SARS-CoV Omicron B.1.1.529 variant by post-immunization serum. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.12.10.21267534v1

[12] SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.12.08.21267417v2

[13] Pfizer and BioNTech Provide Update on Omicron Variant. [press release] *Pfizer and BioNTech.* https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-provide-update-omicron-variant

[14] Booster of mRNA-1273 Vaccine Reduces SARS-CoV-2 Omicron Escape from Neutralizing Antibodies. *medRxiv.* https://www.medrxiv.org/content/10.1101/2021.12.15.21267805v1

following the second dose, and **34-37%** from 15 weeks following the second dose[15]. Nevertheless, results based on preliminary laboratory studies demonstrate that three doses of the Pfizer-BioNTech COVID-19 vaccine neutralize the Omicron variant and increase the antibody titers by **25-fold** compared to two doses[8] and to have an effectiveness against symptomatic infection of **75.5% (95% CI, 56.1-86.3)**[9]. Similar results can also be seen with the administration of other booster doses such as the mRNA-1273 vaccine. Overall, the vaccine-induced immunity of the current COVID-19 vaccines have shown to decrease in comparison to the wild-type and even Delta variant, while the administration of a booster dose has shown to provide a better protection against the new variant.

Results:

Immunogenicity:

Two-doses:

With the newly identified SARS-CoV-2 variant Omicron containing the most mutations thus far, the immunogenicity obtained by COVID-19 vaccines and natural infections might be compromised. This might be the case, as many of the mutations associated with the Omicron variant have been found in areas that are likely bound by neutralizing antibodies. Multiple studies have shown reduced neutralization of SARS-CoV-2 Omicron in previously vaccinated individuals. This is the case of a study performing neutralization assays on sera from seronegative individuals vaccinated with two doses of the Oxford-AstraZeneca vaccine (ChAdOx1) or Pfizer-BioNTech (BNT162b2) vaccine while using an isolate of Omicron obtained from an infected case in the UK (1). The samples of sera were obtained four weeks following the administration of the second dose. Based on the results, the mean neutralization titres of participants who received homologous BNT162b2 **dropped 29.8-fold** for the Omicron variant compared to the wild-type, **10.3-fold** compared to the Beta variant, and **25.1-fold** compared to the Delta variant (1). As for participants who received homologous ChAdOx1, the mean neutralization titres dropped to **below the detectable threshold** in all but one participant (1).

Another study, also examining the neutralization efficacy of vaccine-elicited sera against Omicron, discovered similar results to the previous study. The in vitro study used peripheral blood from double or triple vaccinated individuals who received BNT162b2, mRNA-1273, or ChAdOx1 (2). Based on the results, individuals who received the full jab of BNT162b2 6 months ago had a **11.4-fold reduction** in neutralization against the Omicron variant compared to the Delta variant (from 47% neutralization to 0%, respectively), while individuals who received the full jab of mRNA-1273 6 months ago had a **20-fold reduction** in neuralization against Omicron compared to Delta (from 50% neutralization to

[15] Effectiveness of COVID-19 vaccines against the Omicron (b.1.1529) variant of concern. https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+variant+of+concern.pdf/f423c9f4-91cb-0274-c8c5-70e8fad50074

0%, respectively) (2). An additional study, also analysing the neutralization on BNT162b2, observed that the neutralization of Omicron was **reduced** by **41.4-fold** compared to wild-type leading to **22.5% (95% CI: 8.5%-40.7%)** estimated efficacy against symptomatic infection for individuals vaccinating with BNT162b2 (3).

An additional study using the same methodology as the previous studies examined the neutralization activity against the Omicron variant using the sera of individuals vaccinated, 3 months ago, with the two doses of BNT162b2. Based on the results, a **27-fold reduction** in neutralization was reported against the Omicron variant when comparing it to the wild-type (4).

Another study also examining the neutralizing antibody against the Omicron variant used the sera of fully vaccinated individuals who received the BNT162b2 or the CoronaVac vaccine. Based on the results, only **20% to 24%** of BNT162b2 recipients had detectable neutralizing antibody against the Omicron variant, while **none** of the CoronaVac recipients **had detectable neutralizing antibody titres** against Omicron (5). When evaluating the geometric mean neutralization antibody titres (GMT) of the Omicron variant, BNT162b2 recipients were **35.7- to 39.9-fold lower** than compared to wild-type (5).

Another study analysing neutralizing antibodies titres of sera from convalescent or vaccinated individuals demonstrated that the sera from vaccinated individuals (BNT162b2, mRNA-1273, ChAdOx1) neutralized the Omicron variant much less than any other variant analysed (Alpha, Beta, and Delta) (6). For instance, **1 out of 10** individuals fully vaccinated with mRNA-1273 was seropositive**, 0 out of 20** individuals fully vaccinated with ChAdOx1 were seropositive, **13 out of 20** individuals receiving ChAdOx1 and then BNT162b2 were seropositive, and **9 out of 20** individuals fully vaccinated with BNT162b2 were seropositive against the Omicron variant (6).

Although the neutralization capability against the Omicron variant in fully vaccinated individuals who received two-doses of a COVID-19 vaccine has been clearly reduced, both vaccination and natural infection have been shown to develop T-cell based immunity. Based on a study, analysing the CD8+ T-cell epitomes, the results suggested that the T-cell immune response in previously infected, and possibly vaccinated individuals should still be effective against the Omicron variant (7). Additionally, a study investigating the robustness of T cell responses against Omicron using information of the T cell epitopes known to be targeted in COVID-19 infected or vaccinated individuals reported that a large majority of both CD8+ and CD4+ T cell epitopes appear to remain unaffected by Omicron (8). These results suggest that the effectiveness of pre-existing T cell immunity should remain intact (8).

Booster dose:

For individuals who received a homologous BNT162b2 booster dose 0.5 months ago, the neutralization was reduced by **37.0-fold** against Omicron compared to Delta (from 100% neutralization to 58%, respectively) and for individuals who received their homologous BNT162b2 booster dose 3 months ago, the neutralization was reduced by **24.5-fold** against Omicron compared to Delta (95% neutralization to 25%, respectively) (2). A less severe reduction in neutralization was reported in individuals who received a heterologous booster dose (2 primary doses of mRNA-1273 and BNT162b2 booster). For those individuals who received the booster 0.5 months ago, the neutralization was reduced by **22.7-fold** against Omicron compared to Delta (100% neutralization to 78%, respectively) (2).

A study using authentic virus, multicycle neutralisation assay tried to analyse the ability of sera collected 1, 3, and 6 months post- two doses of BNT162b2 and 4 weeks after receiving the homologous booster dose. Based on the results, the neutralizing antibody titres in the sera examined four weeks after a third dose of BNT162b2 were higher than the ones measured at 1, 3, and 6 months after two doses of BNT162b2. Nevertheless, a **4-fold** reduction in median neutralizing antibodies against Omicron in contrast to the wild-type and a **1.5-fold** decrease against Delta following the third dose were observed (9).

Another study aiming to compare the neutralization of Omicron infected cells by the sera of two-dose and three-dose BNT162b2 vaccinated individuals demonstrated that recipients of a third dose had an increased neutralization efficiency against Omicron (10). Based on the results, the Geometric Mean Titres (GMT) of the wild-type, Beta, Delta, and Omicron were **16.56, 1.27, 8**, and **1.11**, respectively, after receiving two doses of BNT162b2. As for recipients with three doses of the BNT162b2, the GMT of the wild-type, Beta, Delta, and Omicron were **891.4, 152.2, 430.5, and 107.6**, respectively (10). Overall, no neutralization efficiency against Omicron was found in individuals with more than 5 months following the second BNT162b2 dose; however, after a third BNT162b2 dose showed a **100-fold** increase in neutralization efficiency against Omicron with only a **4-fold** reduced neutralization compared to the Delta variant (10).

Another study focusing on the neutralization activity of the mRNA-1273 vaccine against the Omicron variant assessed the potential risk of the variant on the neutralization titres in participants that received two doses or three doses of the mRNA-1273 vaccine (11). In order to test the neutralization titres against the variants, the serum from participants vaccinated with mNRA-1273 were collected and compared in pseudovirus assay in two different laboratories. Based on the results, the geometric mean titres (GMT) after two doses of the vaccine were **84-fold and 49-fold lower** against Omicron in two different laboratories compared to the wild-type and **5.3- and 6.2-fold** less sensitive compared to the Beta variant (11). After the administration of the 50µg mRNA-1273 booster, a **12-fold**

improvement in Omicron neutralization was seen with only a reduction of **6.5- and 4.2-fold** in neutralization against the Omicron variant compared to the wild-type (11). Overall, the Omicron variant was less sensitive to neutralization compared to the wild-type and Beta variant; however, a booster dose increased the Omicron neutralization titres.

Finally, a study examining the neutralization of the three FDA approved vaccines in the United States (mRNA-1273, BNT162b2, Ad26.COV2.S) measured the neutralization potency of sera from 88 mRNA-1273, 111 BNT162b2, and 40 Ad.26.COV2.S vaccine recipients against wild-type, Delta, and Omicron SARS-CoV-2 pseudoviruses (12). The study included individuals that were recently vaccinated (less than 3 months), distantly (6-12 months), or recently boosted with the corresponding homologous vaccine. Based on the results, Omicron neutralization was greatly reduced among all subgroups, including recently vaccinated mRNA-1273 and BNT162b2 recipients (12). For instance, individuals recently vaccinated with mRNA-1273, BNT162b2, and Ad26.COV2.S had a **43-, 122-, and 9-fold reduction** in neutralization titres against Omicron (12). However, recently boosted individuals maintained a potent neutralization of Omicron variant that decreased **6-fold** for mRNA-1273, **4-fold** for BNT162b2, and **13-fold** for Ad26.COV2.S (12). Overall, boosters, especially mRNA vaccines, were shown to broaden neutralizing antibody responses against variants, including Omicron.

Effectiveness:

With the documented decrease in neutralization antibody titers against the Omicron variants, a drop in the effectiveness of the COVID-19 vaccines against the new variant are to be expected. As of right now, various studies have tried estimating the effectiveness of different vaccines against the Omicron variant. One of the studies, assuming a 25-, 80-, and 120-fold decrease in neutralization predicted the effectiveness of two and three BNT162b2 vaccines (13). Based on the results of the study, an effectiveness of **66% (95% CI, 42-86), 48% (95% CI, 25-72), and 42% (95% CI, 20-66)** for up to five months after receiving the two doses was estimated for the 25-, 80-, and 120-fold decrease, respectively (13). As for the effectiveness of three vaccines, **81% (95% CI, 59-95), 67% (95 CI, 43-87), and 61% (95% CI, 37-82)** for up to five months after receiving the booster dose was estimated for 25-, 80-, and 120-fold decrease, respectively (13).

Another study estimating the effectiveness of the BNT162b2 vaccines, estimated that the Omicron variant increased the risk of hospitalization four to five-fold leading to an effectiveness of **84.9% (95% CI, 83.0-86.6)** for recently vaccinated recipients (14). For recipients with reportedly waned effectiveness, the estimated effectiveness was **63.1% (95% CI, 56.9-68.9)** against hospitalization for the Omicron variant (14). As for recipients who received the third dose, the vaccine effectiveness against hospitalization was **91.7% (95% CI, 91.0-92.2)** for the Omicron variant (14). When trying to estimate the vaccine effectiveness against symptomatic disease, an increase in the risk of

symptomatic disease of seven to ten-fold was noticed leading to an estimated effectiveness of **21.4% (95% CI, 17.2-26.4)** against Omicron (14).

A study estimating the vaccine effectiveness against symptomatic disease with 2 doses of BNT162b2 and ChAdOx1, as well as an additional booster dose of BNT162b2 following either the BNT162b2 or ChAdOx1 was conducted in the United Kingdom (15). Based on the results of the study, the vaccine effectiveness against symptomatic disease was lower for Omicron compared to Delta for both vaccines. Among those who received 2 doses of BNT162b2, the vaccine effectiveness was **88.0% (95% CI, 65.9-95.8)** 2 to 9 weeks after the second dose, **48.5% (95%CI, 24.3-65.0)** 10 to 14 weeks after the second dose, and **34 to 37%** 15 weeks after the second dose (15). In regards of the participants who received two doses of the ChAdOx1 vaccines, no protective effect of vaccination was found up to 15 weeks after the second dose. Once a booster dose of BNT162b2 was administered to BNT162b2 recipients, the vaccine effectiveness increased to **75.5% (95% CI, 56.1-86.3)** and to **71.4% (95% CI, 41.8-86.0)** in ChAdOx1 recipients (15). Overall, the vaccine effectiveness dropped in individuals with only two doses of either vaccines, but increase, once again, after receiving the BNT162b2 booster dose.

Another study using previously established model to predict the efficacy for Omicron for immunization with an mRNA vaccine estimated that the Omicron variant waned the efficacy to **40%** against symptomatic and **80%** against severe disease (16). As for the booster dose with an mRNA vaccine, the estimated efficacy would increase up to **86.2% (95% CI, 75.4-92.9)** for symptomatic disease and **98.2% (95% CI, 90.9-99.7)** for severe disease against the Omicron variant (16).

Transmission:

Based on UK's recently published Technical Briefing, **18%** of Omicron index cases gave rise to a secondary household case compared to **10%** of Delta index cases (17). The results were based on a cohort analysis estimating the odds of household transmission for Omicron index cases compared to Delta index cases. After performing a multivariable logistic regression model, the adjusted odds ratio for household transmission from an Omicron index case was **2.9 (95% CI, 2.4-3.5)** compared to Delta index cases (17). As for the secondary attack rates for contacts of cases with Omicron, a secondary attack of **15.8% (95% CI, 14.8-17.5)** was estimated for household exposure, and **8.7% (95% CI, 7.5-10.0)** was estimated for non-household exposure (17). Those results lead to an adjusted odds ratio of **1.96 (1.77-2.16)** for a close contact of Omicron becoming a case compared to Delta index cases (17).

Breakthrough infections:

Recently, a group of German visitors who received three doses of SARS-CoV-2 vaccines, including mRNA vaccine, were confirmed infected with the new Omicron variant. Based on the reported information on the breakthrough infections, all patients experienced symptomatic COVID-19 with mild to moderate reported manifestations. In terms of viral RNA loads, the viral load ranged from 3,69 x 104 copies/mL to 1,65 x 108 copies/mL, while the anti-SARS-CoV-2 spike antibody ranged from 15011 AU / mL to over 40000 AU/mL.

What are the latest updates regarding vaccine waning immunity and duration of protection?

Summary:

Given reports of waning vaccine immunity for all World Health Organization (WHO) Emergency Use Listing (EUL) approved vaccines, it is important to track vaccine effectiveness and duration of protection over time. A US report reported that the proportion of the total US population who were optimally immunized against SARS-CoV-2 fell from a peak of **45.3%** in July 2021 to **29.4%** on November 30 due to declines in vaccine protection over time[16]. Current literature describes various decline in effectiveness among all vaccine types during follow-up studies. Unfortunately, preliminary analysis using Israeli data further demonstrate waning immunity following the third booster dose for all ages[17], however further data and studies are needed to confirm this. Despite reports of reduced effectiveness against SARS-CoV-2 infection with the circulating Delta and newly identified Omicron variant, **vaccine effectiveness continues to remain high against severe infection, hospitalization, and death,** however, the administration of booster doses, vaccination of children, and the encouragement of reducing contacts, social distancing, and mask wearing are recommended in order to mitigate the pandemic effects; A multivariable analysis that assessed the risk of SARS-CoV-2 Delta (B.1.617.2) infection given every day activity, reported that higher risks of infections were observed for individuals who carpool (**aOR:1.3; 95%CI, 1.2-1.4**), travelled by taxi (**aOR:1.5; 95%CI, 1.2-1.8**), subway (**aOR:1.2; 95%CI, 1.0-1.4**), train (**aOR:1.3; 95%CI, 1.1-1.6**), or aeroplane (**aOR:1.7; 95%CI, 1.3-2.2**); recently travelled overseas (**aOR:1.3; 95%CI, 1.1-1.6**); and attended private ceremonies (**aOR:1.7; 95%CI, 1.4-2.2**), bars (**aOR:1.9; 95%CI:1.6-2.2**) or parties (**aOR:3.4; 95%CI:2.8-4.2**)[18] in times of the Delta predominance. Having children was also associated with greater risk of SARS-CoV-2 infection[19]. The summary below covers vaccine waning immunity through the Delta variant period – all Omicron related data are summarised above.

[16] Population optimally immunized after accounting for type-specific COVID-19 vaccine waning intervals: state-level prevalence and trends. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.12.09.21267295v1

[17] Corona virus in Israel – General situation. *Israel Ministry of Health*. https://datadashboard.health.gov.il/COVID-19/general; https://twitter.com/erlichya/status/1467887299753287680

[18] Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France. *The Lancet Regional Health – Europe.* https://www.sciencedirect.com/science/article/pii/S2666776221002647?via%3Dihub

[19] Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France. *The Lancet Regional Health – Europe.* https://www.sciencedirect.com/science/article/pii/S2666776221002647?via%3Dihub

Results:

Vaccine effectiveness against variants

An observational study utilised the Department of Veterans Affairs (VA) national health care database to measure and compare mRNA vaccine effectiveness during the Alpha (participants recruited between 4 January and 14 May) and Delta (participants recruited between 1 July and 20 September) periods (18). Risk ratios were tabulated over a 24-week period (events over 24 weeks per 1,000 persons) for the Alpha variant and over a 12-week period for the Delta variant. Despite both vaccines exhibiting high protection rates against COVID-19 infection, BNT162b2 recipients demonstrated higher risk ratios for testing positive for SARS-CoV-2 than mRNA-1273 recipients, for both the Alpha and Delta predominant periods. The risk difference (BNT162b2 minus mRNA-1273) of documented SARS-CoV-2 infection was **1.23 events** (**95% CI, 0.72-1.81**) per 1,000 persons and **6.54 events** (**95% CI, -2.58-11.82**) per 1,000 persons for the Alpha and Delta periods, respectively (18); the estimated risks over the Delta predominant period were less precise than those calculated over the period of Alpha predominance due to a smaller sample size. These findings are consistent with those of past literature in which Moderna's mRNA-1273 vaccine demonstrated higher protective measures against SARS-CoV-2 when compared to Pfizer-BioNTech's BNT162b2 vaccine (19-22).

Following from Sheikh et al.'s study on BNT162b2 and ChAdOx1 nCoV-19 vaccine effectiveness against Delta (B.1.617.2) infection and hospitalization in Scotland (23), the authors estimated vaccine effectiveness against B.1.617.2-related death from 1 April to 27 September 2021 (24). From a total of 114,706 adults who tested positive for SARS-CoV-2 over that time period, 201 deaths occurred. Vaccine effectiveness against death for individuals aged between 40 and 59 years was estimated at **88% (95% CI, 76-93)** for ChAdOx1 nCoV-19 and **95% (95% CI, 79-99)** for BNT162b2 (24). For older individuals (aged 60 years and above), vaccine effectiveness increased for ChAdOx1 nCoV-19 (**90%; 95% CI, 84-94**) and dropped for BNT162b2 (**87%; 95% CI, 77-93**) (24). Among those aged between 18 and 39 years, 17 deaths occurred among unvaccinated individuals and no deaths occurred in fully vaccinated individuals (24).

Vaccine duration of protection over time

In line with previous data on vaccine duration of protection, the effectiveness of BNT162b2, mRNA-1273, and Ad26.COV2.S against COVID-19 infection declined with the rise of the more transmissible Delta variant in New York. By the week of 28 August vaccine effectiveness against SARS-COV-2 infection had declined to **72.3% (range: 63.7-77.5**), **77.8% (range: 70.1-86.8)**, and **69.4% (range:**

63.4-77.3) for recipients of BNT162b2, mRNA-1273, and Ad26.COV2.S, respectively (25). All three vaccines declined by similar percentage points: **20.7**, **19.5**, and **19.0** percentage points, respectively. Interestingly, younger individuals (18-49 years) demonstrated larger percentage declines (**24.7**; range: **15.5-26.9**) than those aged between 50 and 64 years (median decline of **19.7 percentage points**; range **8.0-21.2**) and 65 years and above (median decline of **14.2 percentage points**; range **5.8-20.3**) (25). Effectiveness against hospitalization, however, remained high between May and August (all vaccines had VEs higher than 80% for all ages and 92% for those aged between 18-64 years), and the authors made the argument that the evidence for waning immunity in their sample was modest (25).

A study in Qatar that estimated BNT162b2's real world effectiveness over the months of December 2020 to September 2021 demonstrated different results to the study conducted in New York. The vaccine reached a peak effectiveness of **77.5% (95% CI, 76.4-78.6**) one month after the second dose and began to gradually decline thereafter (26). The authors reported a rapid decline in vaccine effectiveness from the fourth month (**51.7%; 95% CI, 45.0-57.6**) to the fifth month (**22.5%; 95% CI, 10.6-32.7**) post second dose, reaching an estimated effectiveness of **17.3% (95% CI, 2.2-30.1)** after six months (26). Despite substantial declines in effectiveness against infection, BNT162b2's effectiveness against hospitalization and death remained above 80% over six months, declining from a peak effectiveness of **96.8% (95% CI, 93.9-98.3**) two months post second dose vaccination to **88.9% (95% CI, 52.1-97.4**) after six months. Seven months post vaccination, BNT162b2 immunity dropped to **55.6% (95% CI, -44.3-86.3)**, however, case numbers were small (as per the large confidence interval) and may not be an adequate representative of current real-world effectiveness (26). The authors observed that vaccine waning immunity was **not affected by age nor by differing SARS-CoV-2 variants**. An Israeli study also observed similar waning immunity across all varying age groups. The ratio of infection among fully vaccinated persons was **1.6 (95% CI, 1.3-2.0)**, **1.7 (95% CI, 1.4-2.1)**, **1.6 (95% CI, 1.3-2.0)** higher for persons who were vaccinated 2 months prior to others within their age group, ≥60 years, 40-59 years, and 16-39 years of age, respectively (27). The rate of infection increased to **2.2 (95% CI, 1.3-3.6)** and **2.1 (95% CI, 1.4-3.)** for those aged ≥60 years and 40-59 years, respectively, who were vaccinated 3 months before others in their age category. Owing to vaccinations not being open for those in the 16-39 age category, no risk ratio was able to be calculated for that age group.

A US pre-print evaluated the durability and effectiveness of 2 doses of Moderna's mRNA-1273 vaccine over eight months confirms the vaccine's robust effectiveness over a period of eight months (28). The authors observed moderate waning against SARS-CoV-2 infection from **88%** two months after second dose administration to **75.5%** after 6-8 months, however, effectiveness against COVID-

19 related hospitalization remained stable over eight months (**dropping from 95.9% in 0-2 months to 94.5% in 6-8 months**) (28).

Immunogenicity

A prospective longitudinal cohort study collected anti-SARS-COV-2 antibody titres from **BNT162b2** vaccinated healthcare personnel on a monthly basis in Israel. The median antibody titre collected on the day that the second dose was administered was **885 (95% CI, 33–13827**) **AU/ml**; the median antibody titre increased to **22,266 (95% CI, 571-80,000**) AU/ml one month post second dose administration, and subsequently declined thereafter to **9,682 (95% CI, 2,157-62,491**) **AU/ml** after two months, **2,554 (95% CI, 615-49,653) AU/ml** after three months and to **1,4140 (95% CI, 277-6,103**) **AU/ml** after four months, dropping **57%, 75%,** and **45%**, respectively (29). Median antibody titres were lower for persons older than 50 years (**14,786 ± 15,471 IU/ml**) than individuals younger than 30 years (**33,660 ± 20,771 IU/ml**). The authors observed four breakthrough infections (out of 100 participants), in which all four cases of breakthrough infections had positive high titres prior to confirmed infection (29). A similar Israeli study reported that peak viral titres typically occurred during the first month post full immunization and that immunoglobulin G (IgG) levels reduced substantially each month thereafter, **decreasing by a factor of 18.3 after six months** (30). Neutralizing antibody levels declined at a slower rate, **decreasing by a factor of 3.9** between the first and second month post second dose, and subsequently **decreasing by a factor of 1.2 each month** thereafter until the end of the study period (6 months). The neutralizing antibody mean geometric titre (GMT), expressed as a 50% neutralization titre, was **557.1 (95% CI, 510.8 to 607.7)** one month after the administration of the second dose and decreased to **119.4 (95% CI, 112.0 to 127.3)** after six months (30). Lastly, while a Hong Kong study demonstrated that antibody levels among participants who received BNT162b2 remained over the **50% protection threshold within six months** (31), various reports have described significant waning of vaccine immunogenicity (below protective level) for the BNT162b2 vaccine (32-35), particularly among older vaccinees (30, 36, 37). The same Hong Kong study additionally observed that the protection obtained from two doses of CoronaVac falls below the **50% protection threshold two months** after vaccine administration (31). The progressive decline in immunogenicity among mRNA and viral inactivated vaccines (28, 38-40), calls for the timely administration of vaccine booster doses.

What is influencing breakthrough infections?

Summary:

While all WHO EUL authorised vaccines have demonstrated to be effective against severe SARS-CoV-2 infections and hospitalization, the combined effect of low vaccination rates[20] and waning vaccine immunity[21] has raised concerns. The November *Swiss School of Public Health+* monthly literature report[22] summarised that breakthrough cases are clinically milder[23], are more likely to recover swiftly from illness[24,25], and are less likely to infect others[26,27] compared to unvaccinated persons. Of the few breakthrough cases that require hospitalization, patients often have comorbidities or are immunocompromised[28,29]. To complement last month's summary on breakthrough infections, this December report describes what are the factors influencing breakthrough infections and their transmissibility. Studies have demonstrated that breakthrough infections can occur even when individuals have high levels of vaccine-induced anti-receptor binding domain antibodies[30], are less

[20] Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals. *Nature Medicine*. https://www.nature.com/articles/s41591-021-01407-5

[21] *COVID-19 vaccines and post-vaccination data: Literature update (11).* Swiss School of Public Health. https://www.bag.admin.ch/dam/bag/en/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/Literaturrecherchen/literaturrecherchen_covid-19-impfstoffe_20211130.pdf.download.pdf/FOPH_Literature%20Screening%20report%20Vaccines%2011_20211130.pdf

[22] *COVID-19 vaccines and post-vaccination data: Literature update (11).* Swiss School of Public Health. https://www.bag.admin.ch/dam/bag/en/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/Literaturrecherchen/literaturrecherchen_covid-19-impfstoffe_20211130.pdf.download.pdf/FOPH_Literature%20Screening%20report%20Vaccines%2011_20211130.pdf

[23] Vaccination after prior COVID-19 infection: Implications for dose sparing and booster shots. *EBioMedicine.* https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00379-0/fulltext

[24] Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: A retrospective cohort study. *The Lancet.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02183-8/fulltext

[25] Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2786040

[26] Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. *bioRXiv.* https://www.medrxiv.org/content/10.1101/2021.07.28.21261295v1.full?origin=app

[27] Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA Network.* https://jamanetwork.com/journals/jama/fullarticle/2786040

[28] Understanding breakthrough infections following mRNA SARS-CoV-2 vaccination. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2786040

[29] Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* https://jamanetwork.com/journals/jama/fullarticle/2786039

[30] SARS-CoV-2 infection despite high levels of vaccine-induced anti-Receptor-Binding-Domain antibodies: A study on 1110 health-care professional from a northern Italian University Hospital. *Clinical Microbiology and Infection.* https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00611-X/fulltext

likely to occur in fully (mRNA) vaccinated individuals who had prior SARS-COV-2 infections[31,32,33], and are more likely to occur when living with unvaccinated SARS-CoV-2-infected household members[34]. To further understand the process of breakthrough infections, it would be beneficial to further evaluate the clinical outcomes (particularly the anti-RBD titre) in individuals who become infected post vaccination and identify the differences of memory immunity against SARS-COV-2 across individuals[35].

Results:

Breakthrough case outcomes

Another study compared vaccine breakthrough cases among hospital staff either vaccinated with AZD1222 or BBV152 in India. Among the 325 participants who were vaccinated between January and March 2021, **37 (13.3%)** breakthrough infections were reported until the first week of May. The authors observed that the proportion of breakthrough infections were not influenced by vaccine type, age, sex, history of COVID-19 infection, and adherence to non-pharmaceutical measures (41). Another Indian study that compared in-hospital outcomes between COVID-19 patients who were either vaccinated with COVISHIELD or COVAXIN demonstrated that patients did not demonstrate differences in disease severity or in-hospital mortality by vaccine (42). However, breakthrough infections of COVISHIELD recipients were more likely to have moderate COVID-19 (**29%**) severity compared to COVAXIN (**16.1%; *p*=0.01**), however this could have been influenced by age, as COVISHIELD recipients were older than COVAXIN recipients and were more like to have comorbidities (42). The authors reassure the real-world efficiency of both vaccines in a Delta variant predominant setting.

As highlighted in previous reports and publications, anti-SARS-CoV-2 vaccinations reduce the severity of COVID-19 cases and COVID-19 related hospitalisations. Unvaccinated COVID-19 hospitalised patients demonstrated substantially worse disease progression (higher WHO COVID-19 clinical progression scale and need for oxygen and steroid treatment) and had higher odds of death (**OR: 3.3; 95% CI, 1.05-10.7**) than vaccinated patients. Among those that had to be ventilated the

[31] Association of prior SARS-CoV-2 infection with risk of breakthrough infection following mRNA vaccination in Qatar. *JAMA Network.* https://jamanetwork.com/journals/jama/fullarticle/2785918

[32] Reduced odds of SARS-CoV-2 reinfection after vaccination among New York City Adults, June-August 2021. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.12.09.21267203v1

[33] Implication of SARS-CoV-2 immune escape spike variants on secondary and vaccine breakthrough infections. *Frontiers in Immunology*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8596465/

[34] SARS-CoV-2 infection despite high levels of vaccine-induced anti-Receptor-Binding-Domain antibodies: A study on 1110 health-care professional from a northern Italian University Hospital. *Clinical Microbiology and Infection.* https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00611-X/fulltext

[35] SARS-CoV-2 infection despite high levels of vaccine-induced anti-Receptor-Binding-Domain antibodies: A study on 1110 health-care professional from a northern Italian University Hospital. *Clinical Microbiology and Infection.* https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00611-X/fulltext

odds ratio increased to **54.8 (95% CI, 3.5-852**) (43). Hospitalised vaccinated patients are typically older and have more comorbidities than unvaccinated patients (43-45).

Vaccine effectiveness against breakthrough infections

A study that assessed hospitalization and mortality risk by vaccination type among SARS-CoV-2 breakthrough infections over the months of March until October 2021 (46), demonstrated that when compared to the Pfizer-BioNTech vaccine, the Moderna vaccine had lower adjusted (controlling for age, male sex, comorbidities, and prior SARS-CoV-2 infection) hazard ratios (aHR) for COVID-19 hospitalization (**0.85; 95% CI, 0.74-0.99; *p*<0.05**) while the Janssen vaccine demonstrated higher aHR (**1.78; 95% CI 1.51--2.09; *p*<0.001**) (46). Whereas both mRNA vaccines demonstrated similar aHR for COVID-19 mortality, Janssen recipients had higher risks (**aHR: 1.70; 95% CI; 1.03–2.80, *p*<0.05**) compared to Pfizer-BioNTech. In line with reports of waning vaccine immunity, the proportion of hospitalized breakthrough cases began to increase approximately 110-125 days after full vaccination for all three vaccines; Janssen demonstrated higher rates of hospitalization than the other two mRNA vaccines. Risk of hospitalization and mortality among breakthrough cases were higher for male patients and those of older age (46). In France, vaccine Delta breakthrough infections were not influenced by vaccine type (Pfizer-BioNTech [BNT162b2], Moderna [mRNA-1273], AstraZeneca [ChAdOx1 nCoV-19], Janssen [Ad26.COV2.S], or the heterologous combination of ChAdOx1 nCoV-19/ BNT162b2; *p*=0.362) (47). No differences were observed in the viral cycle threshold (Ct) values between symptomatic and asymptomatic breakthrough cases for the aforementioned vaccines, except for BNT162b2-vaccinated individuals. Symptomatic individuals had lower RT-PCR Ct values (**17.7; 95% CI, 15.07-20.51**) than asymptomatic individuals (**19; 95% CI, 16.00-23.00; *p*=0.004**) (47). Despite studies confirming peak vaccine effectiveness after one month after being fully immunized, 50% of breakthrough infections occurred less than one month after having received two doses, and 75% occurred in patients who were within three months following full immunization. Most infections developed in people aged between 14 and 49 years, most likely due to France's easing of restrictions during the study's measurement period (April to August 2021). Additionally, the proportion of breakthrough infections followed the Delta variant's progression; the highest number of cases occurred during France's Delta peak in August 2021.

Viral dynamics

A study compared SARS-CoV-2 viral dynamics among either vaccinated or unvaccinated participants who were infected with the Alpha (B.1.1.7) or Delta (1.617.2) strains (48). The study found no difference in peak viral load, proliferation duration, clearance duration or duration of acute infection between the two variants and no difference in peak viral load or proliferation of duration between

vaccination status. However, vaccinated persons had shorter viral clearance time (**5.5 days; 95% CI, 4.6-6.5**) compared to unvaccinated persons (**7.5 days; 95% CI, 6.8-8.2**). Similarly, a German study also reported high viral loads (Ct values<10), particularly in the upper airways and lungs, in vaccinated patients who had died of SARS-CoV-2 related complications (49). Fatal cases of COVID-19 in vaccinees were rare and often associated with severe comorbidities or other immunosuppressive conditions. This was accompanied by high rates of pulmonal bacterial or mycotic superinfections and the occurrence of immunocompromising factors such as malignancies, immunosuppressive drug intake, or decreased immunoglobulin levels, indicating a decreased ability to eliminate the virus in patients with an impaired immune system (49). Contrariwise, an Italian study observed clinical and virological differences between COVID-19 breakthrough cases and their respective unvaccinated controls: partially and fully vaccinated (BNT162b2) healthcare staff demonstrated higher prevalence of asymptomatic infections, milder infections, and significantly higher Ct values (partially immunized: **30.3, 95% CI, 24.1-35.5**; fully vaccinated: **35.0, 95% CI, 31.3-35.9**; unvaccinated: **22.3, 95% CI, 19.6-30.6; *p*<0.05**) compared to matched controls (50). Duration of symptoms in breakthrough infections were also shorter in vaccinated individuals (**5 days; 95% CI, 3-6**) than unvaccinated individuals (**9 days; 95% CI, 7-14**) (50).

What is influencing breakthrough infections?

Interestingly, a study that performed logistical regressions comparing Delta and non-Delta breakthrough infections observed that while unmatched analyses showed "elevated numbers of Delta infections in vaccinated compared to unvaccinated individuals", adjusted analyses, correcting for clinical collection date, sex and age, no difference was found between Delta and non-Delta breakthrough infections (51). The Delta variant's predominance rose significantly in metropolitan New York during the study period, so it would come as no surprise if most breakthrough infections that occurred were caused by the B.1.617.2 strain. Nevertheless, the authors' observed that breakthrough infections were weakly associated with spike mutation S112L, nsp12 mutation F192V, and the elimination of seven other mutations across different regions of the SARS-CoV-2 genome (51). Likewise, comorbidities, such as lung disease, cancers, hypertensions, coagulopathy, renal failures, and anaemia, among others, have been continuously reported to be associated with higher risk ratios for developing SARS-CoV-2 breakthrough infections (43-46, 52, 53).

Another study assessed how the "durability of vaccine efficacy contributes to rates of breakthrough infections, especially in the context of evolving variants" (33). Fully vaccinated healthcare workers (HWC) who had positive anti-N titres (confirming SARS-CoV-2 infection) exhibited **2.3-fold higher** mean NT_{50} (p<0.001), against all four SARS-CoV-2 variants – D614G, B.1.17, B.1.351, and B.1.617.2 – than anti-N negative HCWs. Among partially vaccinated HCW, the mean NT_{50} difference was **11.7-**

folder higher (p<0.001). Among those that developed breakthrough infections six months post-vaccination, anti-N positive HCWs had **6.1-fold higher** NT_{50} values than anti-N negative HCWs for all variants (p=0.042). The D614G and Alpha mutations demonstrated greater and more significant differences between anti-N positive and negative NT_{50} titres than the Beta and Delta mutations, "likely due to the strong neutralization resistance of the latter VOCs" (33). The authors also commented that prior SARS-CoV-2 infection correlated to elevated levels of neutralizing antibody (NAb) response once vaccinated (one or two doses), therefore leading to formidable protection against reinfection, corroborating further literature (54, 55).

What is the latest data on COVID-19 booster doses?

Summary:

The characterisation of the durability of protective immunity continues to be one of the toughest challenges many immunologists and vaccinologists are facing. By now, multiple studies and a great deal of evidence have demonstrated that the immunogenicity of fully vaccinated individuals wanes over time, making the implementation of booster vaccination programs crucial for the restoration of immune protection and the reduction of the burden of disease. This issue has been highlighted after the increasing number of breakthrough infections with the Delta variant and the identification of the worrisome new variant of concern Omicron. Multiple countries have approved and started implementing booster vaccination programs to prioritize risk-groups and older individuals, all while expanding the program to include all individuals. Additionally, multiple countries have decided to reduce the minimum interval between the administration of a booster dose from 6 months to 3 months, in face to the new Omicron variant[36]. Based on recent studies, homologous booster doses for the BNT162b2 vaccine have shown to be highly effective against infection and hospitalization, while increasing the neutralizing antibody count higher than the second dose and increasing the IgG antibodies[37]. Additionally, homologous booster doses, especially of BNT162b2, have demonstrated to protect against COVID-19 across all age groups by decreasing the rate of confirmed infections[38]. Heterologous booster doses have also demonstrated to be safe and effective in preventing infections, as demonstrated in a study examining seven different COVID-19 vaccines used as booster doses in people previously vaccinated with AstraZeneca/Oxford or Pfizer-BioNTech vaccines[39]. Although booster doses are becoming more and more crucial in the ongoing battle against COVID-19, the consideration of the substantial geopolitical and ethical implications of booster vaccination programs remain as many individuals in low-income countries have yet to receive the first jabs of COVID-19 vaccines.

Results:

[36] UK's minimum gap for Covid booster jabs to be halved to three months. *The Guardian.* Accessed on: 16/12/2021. https://www.theguardian.com/world/2021/nov/29/covid-booster-jabs-to-be-offered-to-all-uk-adults-after-three-month-gap

[37] Early Immunogenicity and safety of third dose of BNT162b2 mRNA Covid-19 vaccine among adults older than 60years; real world experience. *The Journal of Infectious Diseases.* https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab584/6446235

[38] Protection against Covid-19 by BNT162b2 Booster across Age Groups. *NEJM.* https://www.nejm.org/doi/full/10.1056/NEJMoa2115926

[39] Safety and immunogenicity of seven COVID-19 vaccines as third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomized, controlled, phase 2 trial. *The Lancet.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02717-3/fulltext

Protection & Effectiveness:

Booster doses have shown to increase the protection against confirmed infection, severe illness, and death against COVID-19 as demonstrated by a study using the Israel Ministry of Health database. The study compared the rates of confirmed COVID-19, severe illness, and deaths between individuals who received a BNT162b2 booster dose, at least 12 days earlier, and those who did not received one. Based on the results, the homologous booster dose of BNT162b2 demonstrated to protect against COVID-19 across all age groups by decreasing the rate of confirmed infections by **17.2 (95% CI, 15.4-19.2)** in individuals aged 16-29, by **9.0 (95% CI, 8.4-9.7)** in individuals aged 30-39, by **9.7 (95% CI, 9.2-10.3)** in individuals aged 40-49, by **12.2 (95% CI, 11.4-13.0)** in individuals 50-59, and by **12.3 (95% CI, 11.8-12.8)** in individuals aged 60 and over (56). As for the infection rate, a decrease by a factor of **10.8 (95% CI, 9.6, 12.2)** in individuals aged 16-29, **4.9 (95% CI, 4.5-5.3)** for individuals aged 30-39, **5.4 (95% CI, 5.0-5.8)** in individuals aged 40-49, **7.2 (95% CI, 6.7-7.9)** for individuals aged 50 to 59, and **7.4 (95% CI, 7.0-7.8)** in individuals aged 60 years and older was reported (56). Additionally, the rate of severe illness was also lowered in the booster group compared to the non-boosted group. Based on the study's results, the rate of severe illness was lowered by a factor of **21.7 (95% CI, 10.6-44.2)** in individuals aged 40 to 59 and **17.9 (95% CI, 15.1-21.2)** (56). Finally, when comparing the mortality rate, individuals aged 60 years and older had a lower mortality by a factor of **14.7 (95% CI, 10.0-21.4)** (56). Overall, a homologous booster doses provides an increase in protection across all age groups. Another study, using an Israeli Health Services database, aimed to estimate the adjusted hazard ratio for death due to COVDI-19 in boosted and non-boosted individuals (57). The results concluded that the adjusted hazard ratio for death due to COVID-19 in the booster group, as compared with the non-booster group was **0.10 (95% CI, 0.07-0.14)** meaning that participants who received a homologous booster at least 5 months after the second dose had **90% lower** mortality due to COVID-19 than participants who did not received a booster (57).

The effect of the homologous BNT162b2 booster doses was also demonstrated in a study using the Israel Ministry of Health COVID-19 Dashboard to explore the incidence rates reported per 100,000 regarding SARS-CoV-2 infection and severe illness. Based on the results, the mean daily incidence of infection in individuals younger than 60 years was **66.9 (95% CI, 57.6-76.2)** in the non-booster group compared with **14.8 (95% CI, 11.7-17.9)** in the booster group (corresponding to incidence ratio **of 0.22 [95% CI, 0.22-0.23]**) (58). As for individuals older than 60 years and over, the mean daily incidence was **39.0 (95% CI, 33.9-44.1)** in non-booster and **6.2 (95% CI, 5.2-7.2)** in booster group (incidence ratio of **0.16 [95% CI, 0.15-0.17]**) (58). When examining the incidence rate for severe illness, a mean daily incidence of **0.18 (95% CI, 0.15-0.21)** for individuals aged under 60 years was reported in non-boosted individuals while very few individuals were reported to have severe illness in

the boosted group (58). In people 60 years and older, the mean daily incidence in non-booster was **4.29 (95% CI, 3.86-4.73)** and **0.51 (95% CI, 0.41-0.61)** in the booster group (58).

A retrospective case-control study aiming to calculate the odds of infection with SARS-CoV-2 in people receiving a third dose of BNT162b2 compared to those with only two doses concluded that there was an association between the receipt of a third dose and a reduction in the odds of testing positive for SARS-CoV-2 (59). The study, including data from 1 March 2020 to 4 October 2021, included individuals who were 40 years and older in the study who had received either two doses or three doses of the BNT1162b2 vaccine. Based on the results, an estimated odds ratio of 0.14 (95% CI, 0.13-0.15) 28 to 65 days following the receipt of the booster dose was reported (59). In other words, an 86% reduction in the odds of testing positive for SARS-CoV-2 was seen in individuals with the booster dose (59).

With the reported waning immunity and decrease of effectiveness of COVID-19 vaccines over time, it Is important to evaluate the effectiveness of a third dose. One study evaluating the effectiveness of COVID-29 vaccines and booster doses against infection, hospitalization, and death for the BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), ChAdOx1 (Oxford/AstraZeneca), and Ad26.COV2.S (Janssen) vaccines reported a clear decline in effectiveness for all vaccines over time (60). Nevertheless, with the administration of a booster dose, the effectiveness was restored to similar levels prior to the waning of the effectiveness. Based on the results, regardless of homologous or heterologous booster doses, the BNT162b2 booster dose brought the protection against infection to **92% (95% CI, 91-92),** against hospital admission to **95% (95% CI, 94-96)**, and against death to **97% (95% CI, 96-98)** (60). As for the administration of the mRNA-1273 booster dose, an effectiveness of **93% (95% CI, 91-95)** against infection, **98% (95% CI, 95-99)** against hospital admission, and **close to 100%** against death was reported regardless of homologous or heterologous administration, with the exception of Janssen due to insufficient data (60). Overall, the combination of two mRNA-based vaccines reached a boosted effectiveness of over 91%, while the combination of a mRNA booster and ChAdOx1 showed a somewhat lower effectiveness (60).

Heterologous Booster:

As evidence on the waning immunity and decrease in effectiveness becomes clearer, information on the safety, immunogenicity, efficacy, and effectiveness of booster doses has become crucial. Currently, the majority of data revolves around the administration of homologous booster doses, while very few data on the comparative safety and immunogenicity of different COVID-19 vaccine administered as heterologous boosters exists. Recently, a study aiming to generate data to optimise

the selection of booster vaccines investigated the reactogenicity and immunogenicity of seven COVID-19 vaccines as third doses after two doses of ChAdOx1 or BNT162b2 (61). From 1 June to 30 June 2021, 2878 participants who had received two doses of either ChAdOx1 or BNT162b2 were enrolled in the study and assigned to the COVID-19 vaccine or control group. A total of seven vaccines were distributed across the participants in the COVID-19 vaccine group (Novavax (NVX2373), Oxford/AstraZeneca (ChAdOx1), Pfizer-BioNTech (BNT162b2), Valneva (VLA2001), Janssen (Ad26.COV2.S), Moderna (mRNA1273), and CureVac (CVnCov)). Based on the reactogenicity results, systemic reactions within 7 days after all vaccines were similar, with fatigue and headache the most common systemic reactions, and pain the most frequent local reaction (61). Overall, three vaccines showed increased reactogenicity. As for the results on the immunogenicity of the heterologous booster doses, participants who were previously vaccinated with the two doses of ChAdOx1 had a geometric mean titres (GMT) against the wild-type of **193 GMT (95% CI, 161–231)** after receiving the ChAdOx1 booster, **727 GMT (95% CI, 598–883)** after receiving the Novavax booster, **1621 GMT (95% CI, 1314–1998)** after receiving the BNT162b2 booster, **202 GMT (95% CI, 166–247)** after receiving the Valneva booster, **563 GMT (95% CI, 454–698)** after receiving the Ad26.COV2.S booster, **2368 GMT (95% CI, 2054–2730)** after receiving the mRNA1273 booster, and **373 GMT (95% CI, 310–448)** after receiving the CureVac booster (61). As for participants who were previously vaccinated with the two doses of BNT162b2, the geometric mean titres against the wild-type were **950 GMT (95% CI, 802–1126)** after receiving the ChAdOx1 booster, **766 GMT (95% CI, 624–939)** after receiving the Novavax booster, **1789 GMT (95% CI. 1520–2107)** after receiving the BNT booster, **289 GMT (95% CI, 244–342)** after receiving the Valneva booster, **1441 GMT (95% CI, 1188–1749)** after receiving the Ad26.COV2.S booster, **2019 GMT (95% CI, 1621–2513)** after receiving the mRNA1273 booster, and **487 (95% CI, 411–577)** after receiving the CureVac booster (61).

Another study aiming to appraise the booster effect of the inactivated vaccine (BBIBP), viral vector vaccine (ChAdOx1), and mRNA vaccine (BNT162b2) in healthy individuals who received the inactivated vaccine (CoronaVac) was conducted (62). Regarding the safety, the booster doses were safe with no serious adverse events. As for the immunogenicity, booster doses with the mRNA vaccine had a high proportion of IgG, RBD, and IgA response followed by the viral vector vaccine, while the administration of the inactivated vaccine as a booster had lower booster response, in comparison to the other vaccines (62).

References

1. Dejnirattisai W, Shaw RH, Supasa P, Liu C, Stuart ASV, Pollard AJ, et al. Reduced neutralisation of SARS-COV-2 Omicron-B.1.1.529 variant by post-immunisation serum. medRxiv. 2021:2021.12.10.21267534. https://doi.org/10.1101/2021.12.10.21267534
2. Wilhelm A, Widera M, Grikscheit K, Toptan T, Schenk B, Pallas C, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and monoclonal antibodies. medRxiv. 2021:2021.12.07.21267432. https://doi.org/10.1101/2021.12.07.21267432
3. Cele S, Jackson L, Khan K, Khoury DS, Moyo-Gwete T, Tegally H, et al. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. medRxiv. 2021:2021.12.08.21267417. https://doi.org/10.1101/2021.12.08.21267417
4. Ikemura N, Hoshino A, Higuchi Y, Taminishi S, Inaba T, Matoba S. SARS-CoV-2 Omicron variant escapes neutralization by vaccinated and convalescent sera and therapeutic monoclonal antibodies. medRxiv. 2021:2021.12.13.21267761. https://doi.org/10.1101/2021.12.13.21267761
5. Lu L, Mok B, Chen L, Chan J, Tsang O, Lam B, et al. Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. medRxiv. 2021:2021.12.13.21267668. https://doi.org/10.1101/2021.12.13.21267668
6. Roessler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 B.1.1.529 variant (Omicron) evades neutralization by sera from vaccinated and convalescent individuals. m edRxiv. 2021:2021.12.08.21267491. https://doi.org/10.1101/2021.12.08.21267491
7. Redd AD, Nardin A, Kared H, Bloch EM, Abel B, Pekosz A, et al. Minimal cross-over between mutations associated with Omicron variant of SARS-CoV-2 and CD8+ T cell epitopes identified in COVID-19 convalescent individuals. bioRxiv. 2021:2021.12.06.471446. https://doi.org/10.1101/2021.12.06.471446
8. Ahmed SF, Quadeer AA, McKay M. SARS-CoV-2 T cell responses are expected to remain robust against Omicron. bioRxiv. 2021:2021.12.12.472315. https://doi.org/10.1101/2021.12.12.472315
9. Basile K, Rockett RJ, McPhie K, Fennell M, Johnson-Mackinnon J, Agius J, et al. Improved neutralization of the SARS-CoV-2 Omicron variant after Pfizer-BioNTech BNT162b2 COVID-19 vaccine boosting. bioRxiv. 2021:2021.12.12.472252. https://doi.org/10.1101/2021.12.12.472252
10. Nemet I, Kliker L, Lustig Y, Zuckerman NS, Cohen C, Kreiss Y, et al. Third BNT162b2 vaccination neutralization of SARS-CoV-2 Omicron infection. medRxiv. 2021:2021.12.13.21267670. https://doi.org/10.1101/2021.12.13.21267670
11. Doria-Rose N, Shen X, Schmidt SD, Dell S, McDanal C, Feng W, et al. Booster of mRNA-1273 Vaccine Reduces SARS-CoV-2 Omicron Escape from Neutralizing Antibodies. medRxiv. 2021:2021.12.15.21267805. https://doi.org/10.1101/2021.12.15.21267805
12. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, Lam EC, Nitido AD, Sheehan ML, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. medRxiv. 2021:2021.12.14.21267755. https://doi.org/10.1101/2021.12.14.21267755
13. Volkov O. Predicted Symptomatic Effectiveness of Pfizer-BioNTech BNT162b2 Vaccine Against Omicron Variant of SARS-CoV-2. medRxiv. 2021:2021.12.09.21267556. https://doi.org/10.1101/2021.12.09.21267556
14. Gardner BJ, Kilpatrick AM. Estimates of reduced vaccine effectiveness against hospitalization, infection, transmission and symptomatic disease of a new SARS-CoV-2

variant, Omicron (B.1.1.529), using neutralizing antibody titers. medRxiv. 2021:2021.12.10.21267594. https://doi.org/10.1101/2021.12.10.21267594
15. Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern. medRxiv. 2021:2021.12.14.21267615. https://doi.org/10.1101/2021.12.14.21267615
16. Khoury DS, Steain M, Triccas J, Sigal A, Davenport MP, Cromer D. Analysis: A meta-analysis of Early Results to predict Vaccine efficacy against Omicron. medRxiv. 2021:2021.12.13.21267748. https://doi.org/10.1101/2021.12.13.21267748
17. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England - Technical briefing 32. 2021 17 December 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042046/Technical_Briefing_32.pdf.
18. Dickerman BA, Gerlovin H, Madenci AL, Kurgansky KE, Ferolito BR, Figueroa Muñiz MJ, et al. Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2115463
19. Puranik A, Lenehan PJ, Silvert E, Niesen MJM, Corchado-Garcia J, O'Horo JC, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv. 2021:2021.08.06.21261707. https://doi.org/10.1101/2021.08.06.21261707
20. Bajema KL, Dahl RM, Prill MM, Meites E, Rodriguez-Barradas MC, Marconi VC, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19-Associated Hospitalization - Five Veterans Affairs Medical Centers, United States, February 1-August 6, 2021. MMWR Morbidity & Mortality Weekly Report. 2021;70(37):1294-9. https://doi.org/10.15585/mmwr.mm7037e3
21. Self WH, Tenforde MW, Rhoads JP, Gaglani M, Ginde AA, Douin DJ, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021. Morbidity & Mortality Weekly Report. 2021;70(38):1337–43. https://doi.org/10.15585/mmwr.mm7038e1
22. Rodriguez Velásquez S, Guizzo Dri G. COVID-19 vaccines and post-vaccination data: Literature update (9). Geneva: Swiss School of Public Health; 2021. Contract No.: 9. https://www.bag.admin.ch/dam/bag/en/dokumente/mt/k-und-i/aktuelle-ausbrueche-pandemien/2019-nCoV/Literaturrecherchen/literaturrecherchen-covid-19-impfstoffe-20210830.pdf.download.pdf/20210830_Literaturrecherchen_Covid-19-Impfstoffe_EN.pdf.
23. Sheikh A, McMenamin J, Taylor B, Robertson C. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. The Lancet. 2021;397(10293):2461-2. https://doi.org/10.1016/S0140-6736(21)01358-1
24. Sheikh A, Robertson C, Taylor B. BNT162b2 and ChAdOx1 nCoV-19 Vaccine Effectiveness against Death from the Delta Variant. New England Journal of Medicine. 2021;385(23):2195-7. https://doi.org/10.1056/NEJMc2113864
25. Rosenberg ES, Dorabawila V, Easton D, Bauer UE, Kumar J, Hoen R, et al. Covid-19 Vaccine Effectiveness in New York State. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2116063
26. Chemaitelly H, Tang P, Hasan MR, AlMukdad S, Yassine HM, Benslimane FM, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. New England Journal of Medicine. 2021;385(24):e83. https://doi.org/10.1056/NEJMoa2114114
27. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning Immunity after the BNT162b2 Vaccine in Israel. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2114228

28. Florea A, Sy LS, Luo Y, Qian L, Bruxvoort KJ, Ackerson BK, et al. Durability of mRNA-1273 against COVID-19 in the time of Delta: Interim results from an observational cohort study. medRxiv. 2021:2021.12.13.21267620. https://doi.org/10.1101/2021.12.13.21267620
29. Khoury J, Najjar-Debbiny R, Hanna A, Jabbour A, Abu Ahmad Y, Saffuri A, et al. COVID-19 vaccine - Long term immune decline and breakthrough infections. Vaccine. 2021;39(48):6984-9. https://doi.org/10.1016/j.vaccine.2021.10.038
30. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning Immune Humoral Response to BNT162b2 Covid-19 Vaccine over 6 Months. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2114583
31. Kwok SLL, Cheng SMS, Leung JNS, Leung K, Lee C-K, Wu JT, et al. Waning antibody levels after vaccination with mRNA BNT162b2 and inactivated CoronaVac COVID-19 vaccines in Hong Kong blood donors. medRxiv. 2021:2021.12.05.21267330. https://doi.org/10.1101/2021.12.05.21267330
32. Achiron A, Mandel M, Dreyer-Alster S, Harari G, Gurevich M. Humoral SARS-COV-2 IgG decay within 6 months in COVID-19 healthy vaccinees: The need for a booster vaccine dose? Eur J Intern Med. 2021;94:105-7. https://doi.org/10.1016/j.ejim.2021.10.027
33. Evans JP, Zeng C, Carlin C, Lozanski G, Saif LJ, Oltz EM, et al. Loss of Neutralizing Antibody Response to mRNA Vaccination against SARS-CoV-2 Variants: Differing Kinetics and Strong Boosting by Breakthrough Infection. bioRxiv. 2021:2021.12.06.471455. https://doi.org/10.1101/2021.12.06.471455
34. Ferrari D, Clementi N, Criscuolo E, Ambrosi A, Corea F, Di Resta C, et al. Antibody Titer Kinetics and SARS-CoV-2 Infections Six Months after Administration with the BNT162b2 Vaccine. Vaccines (Basel). 2021;9(11). https://doi.org/10.3390/vaccines9111357
35. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, et al. Neutralising antibody activity against SARS-CoV-2 VOCs B.1.617.2 and B.1.351 by BNT162b2 vaccination. The Lancet. 2021;397(10292):2331-3. https://doi.org/10.1016/S0140-6736(21)01290-3
36. Salvagno GL, Henry BM, Pighi L, De Nitto S, Gianfilippi G, Lippi G. The pronounced decline of anti-SARS-CoV-2 spike trimeric IgG and RBD IgG in baseline seronegative individuals six months after BNT162b2 vaccination is consistent with the need for vaccine boosters. Clinical Chemistry and Laboratory Medicine. 2021. https://doi.org/10.1515/cclm-2021-1184
37. Kawasuji H, Morinaga Y, Tani H, Saga Y, Kaneda M, Murai Y, et al. Age-Dependent Reduction in Neutralization against Alpha and Beta Variants of BNT162b2 SARS-CoV-2 Vaccine-Induced Immunity. Microbiol Spectr. 2021:e0056121. https://doi.org/10.1128/Spectrum.00561-21
38. Zhong D, Xiao S, Debes AK, Egbert ER, Caturegli P, Colantuoni E, et al. Durability of Antibody Levels After Vaccination With mRNA SARS-CoV-2 Vaccine in Individuals With or Without Prior Infection. Jama. 2021. https://doi.org/10.1001/jama.2021.19996
39. Woldemeskel BA, Garliss CC, Blankson JN. mRNA Vaccine-Elicited SARS-CoV-2-Specific T cells Persist at 6 Months and Recognize the Delta Variant. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021. https://doi.org/10.1093/cid/ciab915
40. Sariol CA, Serrano-collazo C, Ortiz EJ, Pantoja P, Cruz L, Arana T, et al. Limited impact of delta variant's mutations on the effectiveness of neutralization conferred by natural infection or covid-19 vaccines in a latino population. Viruses. 2021;13(12). https://doi.org/10.3390/v13122405

41. Sharma P, Mishra S, Basu S, Kumar R, Tanwar N. Breakthrough Infection With Severe Acute Respiratory Syndrome Coronavirus 2 Among Healthcare Workers in Delhi: A Single-Institution Study. Cureus. 2021;13(10):e19070. https://doi.org/10.7759/cureus.19070
42. Suri TM, Ghosh T, M A, Vadala R, Vig S, Bhatnagar S, et al. In-hospital mortality due to breakthrough COVID-19 among recipients of COVISHIELD (ChAdOx nCoV-19) and COVAXIN (BBV152). medRxiv. 2021:2021.12.07.21267398. https://doi.org/10.1101/2021.12.07.21267398
43. Padovani A, Cristillo V, Tomasoni D, Gipponi S, Pilotto A. SARS-CoV-2 vaccination predicts COVID-19 progression and outcomes in hospitalized patients. medRxiv. 2021:2021.11.21.21266633. https://doi.org/10.1101/2021.11.21.21266633
44. Juthani PV, Gupta A, Borges KA, Price CC, Lee AI, Won CH, et al. Hospitalisation among vaccine breakthrough COVID-19 infections. Lancet Infect Dis. 2021. https://doi.org/10.1016/s1473-3099(21)00558-2
45. Parums DV. Editorial: SARS-CoV-2 Vaccine Responses and Breakthrough COVID-19. Med Sci Monit. 2021;27:e935624. https://doi.org/10.12659/msm.935624
46. Kshirsagar M, Mukherjee S, Nasir M, Becker N, Ferres JL, Richardson BA. Risk of hospitalization and mortality after breakthrough SARS-CoV-2 infection by vaccine type and previous SARS-CoV-2 infection utilizing medical claims data. medRxiv. 2021:2021.12.08.21267483. https://doi.org/10.1101/2021.12.08.21267483
47. Bal A, Destras G, Simon B, Giannoli J-M, Morfin-sherpa F, Lina B, et al. Investigation of Vaccine Breakthrough Infections by Vaccine strategy during the Delta Variant Wave in France. medRxiv. 2021:2021.12.05.21267301. https://doi.org/10.1101/2021.12.05.21267301
48. Kissler SM, Fauver JR, Mack C, Tai CG, Breban MI, Watkins AE, et al. Viral Dynamics of SARS-CoV-2 Variants in Vaccinated and Unvaccinated Persons. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMc2102507
49. Hirschbuehl K, Schaller T, Maerkl B, Claus R, Sipos E, Rentschler L, et al. High viral loads: what drives fatal cases of COVID-19 in vaccinees? an autopsy study. medRxiv. 2021:2021.12.03.21267155. https://doi.org/10.1101/2021.12.03.21267155
50. Trunfio M, Verga F, Ghisetti V, Burdino E, Emanuele T, Bonora S, et al. Clinical phenotype and contagiousness of early breakthrough SARS-CoV-2 infections after BNT162b2 COVID-19 mRNA vaccine: A parallel cohort study in healthcare workers. Vaccines. 2021;9(12). https://doi.org/10.3390/vaccines9121377
51. Duerr R, Dimartino D, Marier C, Zappile P, Levine S, Francois F, et al. Clinical and genomic signatures of rising SARS-CoV-2 Delta breakthrough infections in New York. medRxiv. 2021:2021.12.07.21267431. https://doi.org/10.1101/2021.12.07.21267431
52. Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association between mRNA Vaccination and COVID-19 Hospitalization and Disease Severity. JAMA - Journal of the American Medical Association. 2021. https://doi.org/10.1001/jama.2021.19499
53. Klompas M. Understanding Breakthrough Infections following mRNA SARS-CoV-2 Vaccination. JAMA - Journal of the American Medical Association. 2021. https://doi.org/10.1001/jama.2021.19063
54. Levin-Rector A, Firestein L, McGibbon E, Sell J, Lim S, Lee EH, et al. Reduced Odds of SARS-CoV-2 Reinfection after Vaccination among New York City Adults, June–August 2021. medRxiv. 2021:2021.12.09.21267203. https://doi.org/10.1101/2021.12.09.21267203
55. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, Yassine HM, Benslimane FM, Al Khatib HA, et al. Association of Prior SARS-CoV-2 Infection with Risk of Breakthrough Infection following mRNA Vaccination in Qatar. JAMA - Journal of the American Medical Association. 2021;326(19):1930-9. https://doi.org/10.1001/jama.2021.19623

56. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection against Covid-19 by BNT162b2 Booster across Age Groups. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2115926
57. Arbel R, Hammerman A, Sergienko R, Friger M, Peretz A, Netzer D, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. New England Journal of Medicine. 2021. https://doi.org/10.1056/NEJMoa2115624
58. Bomze D, Sprecher E, Gamzu R. Effect of a nationwide booster vaccine rollout in Israel on SARS-CoV-2 infection and severe illness in young adults. Travel Med Infect Dis. 2021;44:102195. https://doi.org/10.1016/j.tmaid.2021.102195
59. Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JL, Weinberger DM. Odds of Testing Positive for SARS-CoV-2 following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine. JAMA Internal Medicine. 2021. https://doi.org/10.1001/jamainternmed.2021.7382
60. Berec L, Smid M, Pribylova L, Majek O, Pavlik T, Jarkovsky J, et al. Real-life protection provided by vaccination, booster doses and previous infection against covid-19 infection, hospitalisation or death over time in the Czech Republic: a whole country retrospective view. medRxiv. 2021:2021.12.10.21267590. https://doi.org/10.1101/2021.12.10.21267590
61. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet. 2021. https://doi.org/10.1016/s0140-6736(21)02717-3
62. Kanokudom S, Assawakosri S, Suntronwong N, Auphimai C, Nilyanimit P, Vichaiwattana P, et al. Safety and immunogenicity of the third booster dose with inactivated, viral vector, and mRNA COVID-19 vaccines in fully immunized healthy adults with inactivated vaccine. medRxiv. 2021:2021.12.03.21267281. https://doi.org/10.1101/2021.12.03.21267281