

SARS-CoV-2 infections in fully vaccinated versus unvaccinated individuals

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Abstract

Background. The Covid-19 pandemic is one of the most live-disturbing crises of this century. With the achievement of high vaccination coverage in high-income countries the pandemic has entered a new phase. Many countries have implemented 'corona passports' for traveling and/or access to specific businesses. Unvaccinated individuals can obtain such passport if they have either proof of recovery from corona or a negative test. There has been much debate about the value of these Covid certificates, in particular whether testing unvaccinated but not fully vaccinated individuals is reasonable and supported by scientific evidence. Viral loads in fully vaccinated individuals with breakthrough infections have been shown to be similar to those in unvaccinated people with a first infection. While some studies provide evidence that the odds of breakthrough infection are lower than of first infection in unvaccinated persons, these studies were conducted in specific populations. In this study data from Israel from 20 December 2020 till 4 September 2021 covering the entire general population is used to assess the vaccine effectiveness (VE) over time.

Methods. Publicly available data is retrieved from the Israeli government information site and Israeli Central Bureau of Statistics. For each week between 20 December 2020 and 4 September 2021 the VE is calculated for age groups 0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and 90+. In addition, the VE for hospitalization and for death are calculated per week per age group.

Results. While initially the VEs in each age group are around 90%, in mid-June 2021 the VEs show a rapid decline, reaching zero or even negative values in the fourth week of June 2021 and remain close to zero until mid-August 2021. The decline of VEs coincides with the moment that the Delta variant became dominant. The absolute number of positive tests is high between mid-July and mid-August 2021, providing relative robust VE estimates. With VEs around zero in this period, this provides relative strong evidence that fully vaccinated individuals are equally at risk of infection as unvaccinated individuals. Since 15 August 2021 the VEs started to increase, coinciding with the administration of a third dose. The recovery of VEs is proportional to the percentage of people who have received the third shot per age group. While the VEs for a positive test declined and reach values around or below zero, the VEs for hospitalization and death remained relatively high over the entire period.

Conclusions. This analysis shows that in the Delta-dominated period in Israel fully vaccinated individuals are equally susceptible to infection as unvaccinated people. This does not support a regime in which only unvaccinated people are tested in order to curb infections, nor exclusion of unvaccinated individuals from activities to prevent spreading of SARS-CoV-2.

The effectiveness of vaccination to prevent infections seems to be boosted by a third shot, although there is no long term data available that enables conclusions on the duration of this effect.

Reassuringly, the analysis shows that vaccination has continued to offer good protection against hospitalization and death.

The Covid-19 pandemic is one of the most live-disturbing crises of this century. By the end of 2020 the first vaccine received conditional market authorization in Europe by the European Medicines Agency (EMA) and emergency use authorization in the U.S. by the Food and Drug Administration (FDA). Similar authorizations were issued in other countries. Vaccination programs were rapidly put in place, in particular in high-income countries, and since this moment the pandemic has entered a new phase.

Many countries implemented 'corona passports' for traveling and/or access to specific businesses such as restaurants and theaters. For example, in Europe the "EU Digital COVID Certificate" has entered into application on 1 July 2021 [1]. Like many national implementations, this certificate is issued if one of three conditions is met: the person has (1) been vaccinated against COVID-19, (2) recovered from COVID-19, or (3) received a negative test result. Unvaccinated individuals can use the latter two options. Some countries, such as Germany, are planning to omit the third option, effectively excluding unvaccinated people from certain activities [2].

There has been much debate about the value of these Covid certificates. One important question is whether testing unvaccinated but not fully vaccinated individuals is reasonable and supported by scientific evidence. While testing may detect potentially infectious individuals and prevent transmission, people who have been fully vaccinated may be infectious as well yet are exempted from testing. Indeed, recent studies have indicated that in people without previous SARS-CoV-2 infections fully vaccinated individuals with breakthrough infections have similar viral loads as unvaccinated individuals [3–7]. The occurrence of breakthrough infections may be attributed to either the emergence of the Delta variant (B.1.617.2) or waning immunity. Despite viral loads of breakthrough infections in fully vaccinated people are similar to those in unvaccinated people, the odds of a breakthrough infection may be lower than that of infection in the unvaccinated population. Indeed, despite being lower than initially reported in randomized controlled trials, the vaccine effectiveness (VE) of BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) vaccines against asymptomatic or symptomatic infections among frontline workers was recently reported to be 66% [8]. Similarly, the VE for infection in nursing home residents setting during the Delta-dominated period was reported to be 53.1% [9]. However, the aforementioned studies were conducted in specific populations and limited in population size and may not be representative for the general population.

In order to assess the development over time of the risk of infection in fully vaccinated people versus unvaccinated people, another approach may be to use publicly available country-level data. Many countries conduct and publish weekly or daily number of positive RT-PCR tests for SARS-CoV-2, as well as data on vaccination. In this report, data from Israel is used for this assessment. Israel provides publicly available data on positive tests and events per vaccination status and per age group, as well as the number of people who have received one, two, or three vaccines doses over time per age group. Moreover, Israel was one of the first countries in the world to obtain high vaccination coverage and to employ booster shots. Given the recent surge in infections in Israel [10], data from this country can reveal the VE in a real-world environment with high vaccination coverage. The analysis focuses on VE for a positive test, but VE for hospitalization and death is assessed as well.

Methods

Test, events, and vaccination data was retrieved from the Israeli government information site (data.gov.il) and population data from the Israeli Central Bureau of Statistics (cbs.gov.il/en) on 15 September 2021.

The test dataset¹ consists of the number of positive tests per week for the age groups 0-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and 90+, stratified for the following vaccination statuses: 1-6 days after 1st dose, 7-13 days after 1st dose, 14-20 days after 1st dose, above 20 days after 1st dose, 1-6 days after 2nd dose, 7-13 days after 2nd dose, 14-20 days after 2nd dose, above 20 days after 2nd dose, 1-6 days after 3rd dose, 7-13 days after 3rd dose, 14-20 days after 3rd dose, above 20 days after 3rd dose, unvaccinated. The number of positive tests per group is reported from 20 December 2020 till 4 September 2021. In the analyses fully vaccinated are considered those who have received the second dose 14 days or more before a positive test, including those who have received a third dose. This is compared to the number of positive tests in the unvaccinated group. The number of positive tests in those who have received the second dose less than 14 days before the positive test or who have received only one dose are omitted.

The events dataset² contains the number of hospitalization and death events per week in people who have received one, two, or three doses or are unvaccinated in the same age groups as used for the number of positive tests. The events dataset contains all events from 20 December 2021 till 11 September 2021. In the analysis events in fully vaccinated are considered all events in those who have received two or three doses.

The vaccination dataset³ contains daily number of first, second, or third doses administrated in the same age groups as used for the number of positive tests from 20 December 2021 till 11 September 2021. For the analysis the number of people who have received their second dose at least 14 days prior are calculated for each week to obtain the cumulative number of fully vaccinated people per week per age group. In addition, the number of partially vaccinated per week per age group is calculated as the sum of people who have received their first dose 21 days prior and people who received their second dose less than 14 days prior. For the first dose 21 days was used, because in Israel the second dose is administered after this period [11].

The population size data set⁴ was published on 4 July 2021 and contains the Israeli population size of each age (per year) in 2020. This is used to determine the total size of each of the aforementioned age groups.

Using the above data, for each week the total number of fully vaccinated and unvaccinated people in each age group is calculated. The latter is calculated from the total population size of the age group minus the number of partially and fully vaccinated people. The number of positive tests in fully vaccinated and unvaccinated people per age group is divided by the population size of the fully

¹ <https://data.gov.il/dataset/covid-19/resource/9b623a64-f7df-4d0c-9f57-09bd99a88880>

² <https://data.gov.il/dataset/covid-19/resource/8a51c65b-f95a-4fb8-bd97-65f47109f41f>

³ <https://data.gov.il/dataset/covid-19/resource/57410611-936c-49a6-ac3c-838171055b1f>

⁴ <https://www.cbs.gov.il/en/publications/Pages/2021/Population-Statistical-Abstract-of-Israel-2021-No.72.aspx>, table 2.3

vaccinated and unvaccinated people in each age group respectively for that week to obtain the percentage of people who tested positive in these strata. From these numbers, the VE per age group per week is calculated as:

$$VE = 100\% * (1 - \text{perc_pos_fully_vaccinated}_{\text{week}_n} / \text{perc_pos_unvaccinated}_{\text{week}_n})$$

If $\text{perc_pos_unvaccinated}_{\text{week}_n}$ is 0, VE is set to 100%.

For visualizing the percentage of sequences with the Delta variant the Github dataset⁵ from CoVariants.org (<https://covariants.org>) was retrieved on 16 September 2021.

All calculations were performed and all graphs were created in Microsoft Excel 2019.

Results

In Figure 1 the VE for a positive test per week per age group is shown. Between the start of vaccination (end of December 2020) until mid-June 2021 the calculated VE in each age group is around 90%. In December 2020 and January 2021 (not shown) some variation occurs, which are most likely numerical artefacts due low numbers of fully vaccinated people in those months (Figure S1). In mid-June 2021 the VE shows a rapid decline in all age groups between 20 and 69, reaching zero or even negative values in the fourth week of June 2021. Although the VEs in these age groups recover a couple of weeks later, they remain close to zero until mid-August 2021.

In age groups 0-19 and 70-79, 80-89, and 90+ the VEs also start declining, but at a later point in time. Eventually the VE in each of these age groups drops below 20% at some point in time, but here too the VEs recover from end of July onwards. In all age groups the recovery of VE continues until the last week in the dataset (29 August till 4 September 2021), but, except for the age group 70-79, none of the VEs for a positive test have (yet) reached 90% again.

The moment that the VEs starting declining coincides with the moment that the Delta variant became dominant. On 31 March 2021 68% of all sequences samples was identified as the Delta variant and this increased to 98% on 14 June 2021 and has continued to be above 90% since (figure S3). In the beginning of June 2021, the percentage of the population that was tested positive was very low (Figure 2). Remarkably, the percentage of the population with a positive test started to increase exponentially with approximately the same onset and slope in each age group after the Delta variant became dominant (Figure 2). The negative VEs for a positive test in age groups 20-69 occurred when the absolute number of positive tests were very low (Figure S3). For example, in the week of 20 June 2021 the VE in the age group 50-59 was -162%, but the absolute number of positive tests were only 75 in the fully vaccinated group and 5 in the unvaccinated group. However, in the week of 8 August the VE in this age group was 0% and close to zero in age groups 20-29, 30-39, 40-49, and 60-69 too, while the weekly absolute number of positive test in age group 50-59 were 2903 and 482 in fully vaccinated and unvaccinated people respectively. The high number of positive tests between mid-July and mid-August 2021 provide a

⁵ https://raw.githubusercontent.com/hodcroftlab/covariants/master/cluster_tables/EUClusters_data.json

relative strong indication that fully vaccinated individuals were equally at risk of infection as unvaccinated individuals.

In the week of 25 July 2021 Israel started to inoculate the population with a third dose. For age groups 60-90+ the campaign rapidly led to a high percentage with a third dose, reaching 49-67% by 15 August 2021 (Figure 3). This coincides with increasing VEs for a positive test in these age groups (Figure 1). For example, in age group 60-69 the VE increased from -57% in the week of 25 July 2021 to 25% in the week of 15 August 2021, to 67% in the week of 29 August 2021, coinciding with 0%, 48.8% and 65.4% of that age group that had received a third dose respectively. In line with this, the percentage of the population with a positive test started declining in these age groups after 8 August 2021. This indicates that, even though the VEs have not (yet) reached their initial high values of >90%, the third dose seems to have boosted the VEs for a positive test to values around 70-80%.

While the VEs for a positive test declined and reach values around or below zero, the VEs for hospitalization and death remained relatively high (Figures S4 and S5). The VEs for hospitalized do show a decrease, which occurred a couple of weeks later than the decline of VEs for a positive test, but remains above 50% for most age groups at all times (Figure S4). The VE for hospitalization recovers after the week of 8 August 2021 in all age groups, reaching values around 80-90% in most age groups in the week of 29 August 2021. Similarly, the VEs for death decline somewhat in the 60+ age groups, but never drop below 65% (Figure S5). The drop is shifted a couple of week compared to the drop in hospitalization and recovers to values around 85-95% in the week of 29 August 2021. This indicates that vaccination still effectively protects against hospitalization and death.

Discussion

This analysis shows that, while the VE for a positive test was initially high, it rapidly dropped in all age groups when the Delta variant became dominant. Although the low and even negative values of the VE for a positive test at the start of the Delta surge may not provide an accurate representation due to the low absolute number of positive tests, the VEs between mid-July and mid-August 2021 are based on relatively high absolute number of positive tests. In the latter period the VE in the age group 20-69 (representing 56% of the complete Israeli population) was around zero. This indicates that during this Delta-dominated period fully vaccinated individuals were equally susceptible to infection as unvaccinated people. Combined with the evidence that fully vaccinated persons with breakthrough infections have a similar viral load as unvaccinated people with a first infection [3–7], this indicates that testing unvaccinated but not fully vaccinated individuals is not supported by a higher susceptibility to infection of unvaccinated individuals in a Delta-dominated situation. When the majority of a population is fully vaccinated, equal susceptibility to infection means that the majority of transmission occurs in fully vaccinated persons.

Although some evidence indicates that the infectious period is shorter in fully vaccinated individuals with a breakthrough infection than in unvaccinated with a first infection, this period is at least a week in both groups, based on $Ct \leq 25$ [12]. This does not seem to provide a sound basis to exempt fully vaccinated but not unvaccinated individuals from testing.

Reassuringly, although the VEs for a positive test declined, the VEs for hospitalizing and death have remained high. Although in the week of 1 August 2021 the absolute number of hospitalized people who had received two or three doses was almost twice as much as the absolute number of hospitalizations of unvaccinated persons (457+10 vs 255, Figure S6), the average VE for hospitalization was still 70-80% in that week. Thus, the risk of hospitalization is lowered by vaccination.

This analysis also shows that, at least temporarily (by lack of long term data), a third dose seems to boost the VE for a positive test. The percentages of the population that received a positive test result seem to have been curbed in the various age groups proportional to the percentage of people who have received a third dose in each age group. This may indicate that, rather than a reduced effectiveness against the Delta variant, the cause of the surge in cases is due to waning immunity. That is, the third dose is identical to the first and second and does seem to be able to curb infections with the Delta variant where full vaccination with two doses did not. This is in line with the conclusion by Bar-On *et al* who reported that the third dose provides a substantially better effectiveness against infection than two doses [13]. It remains to be determined how long-lasting this boosting effect is.

This analysis has a number of limitations. First, the population size data stems from 2020. The Israeli dashboard uses population size data from April 2021, yielding lower vaccination coverage values than calculated in this analysis (Table S1). This indicates that the population size in the various age groups have increased, which is in line with Israel's growing population [14]. If the vaccination coverage is lower, the VEs will be lower.

Second, the data may be confounded by differences in testing regime. The number of tests in each group (fully vaccinated vs. unvaccinated) is unknown and it cannot be verified if this is evenly distributed. An uneven distribution may increase the probability of detecting a case and therewith the total number of positive tests in that group. It may be argued that unvaccinated individuals may have tested more often than fully vaccinated people because for unvaccinated individuals a negative test provides access to activities and a positive test can be used later as proof of recovery after infection. This would bias the estimated VE in favor of the fully vaccinated group. The fact that the percentage of the population of each age group with a positive test showed very similar values per week and very similar growth rates between mid-June and 8 August 2021 (Figure 2), may indicate that infections were evenly distributed among the population. Since the vaccination coverage in the various age groups is different, this supports the conclusion that fully vaccinated individuals were equally susceptible to infection as unvaccinated persons in that time period.

Third, no data is available about the number of individuals per week that have recovered from infection. Even if data of tested individuals would be available, this would not include people who were infected and recovered without being tested (e.g. asymptomatic cases). Recent evidence shows that previously infected individuals who have not been vaccinated have a lower risk of reinfection than fully vaccinated SARS-CoV-2-naïve individuals [15]. This can confound the data of positive tests in unvaccinated individuals. Similarly, a proportion of fully vaccinated individuals may have had previous infection or multiple breakthrough infections, confounding the data of positive tests in fully vaccinated individuals. The latter confounding is deemed less likely than the former, which means that the estimate may be biased in favor of unvaccinated people.

Fourth, the vast majority of vaccinated people received the BioNTech/Pfizer mRNA BNT162b2 vaccine [10]. Therefore, this analysis only applies to this particular vaccine and it cannot be concluded whether or not the same results would be found in a population with mixed or other vaccines.

The strength of this analysis is that data from an entire country is used, consisting of a population at risk of 9.2 million people. The VE estimates are based on a real-world setting, using the general population.

Second, the size of the dataset means that a relatively large number of cases is observed, providing a more robust estimate of VE.

Third, the analysis uses data of a population with high vaccination coverage, where the strongest effect of vaccination can be expected.

Fourth, the usage of publicly available data that is well-maintained allows easy repeat of this analysis, as well as semi-real time tracking how things evolve.

Conclusions

This analysis shows that during the Delta-dominated period in Israel fully vaccinated individuals were equally susceptible to infection as unvaccinated people. This does not support a regime in which only unvaccinated people are tested in order to curb infections, nor exclusion of unvaccinated individuals from activities to prevent spreading of SARS-CoV-2.

The effectiveness of vaccination to prevent infections seems to be boosted by a third shot, although there is no long term data available that enables conclusions on the duration of this effect.

Reassuringly, the analysis shows that vaccination has continued to offer good protection against hospitalization and death.

References

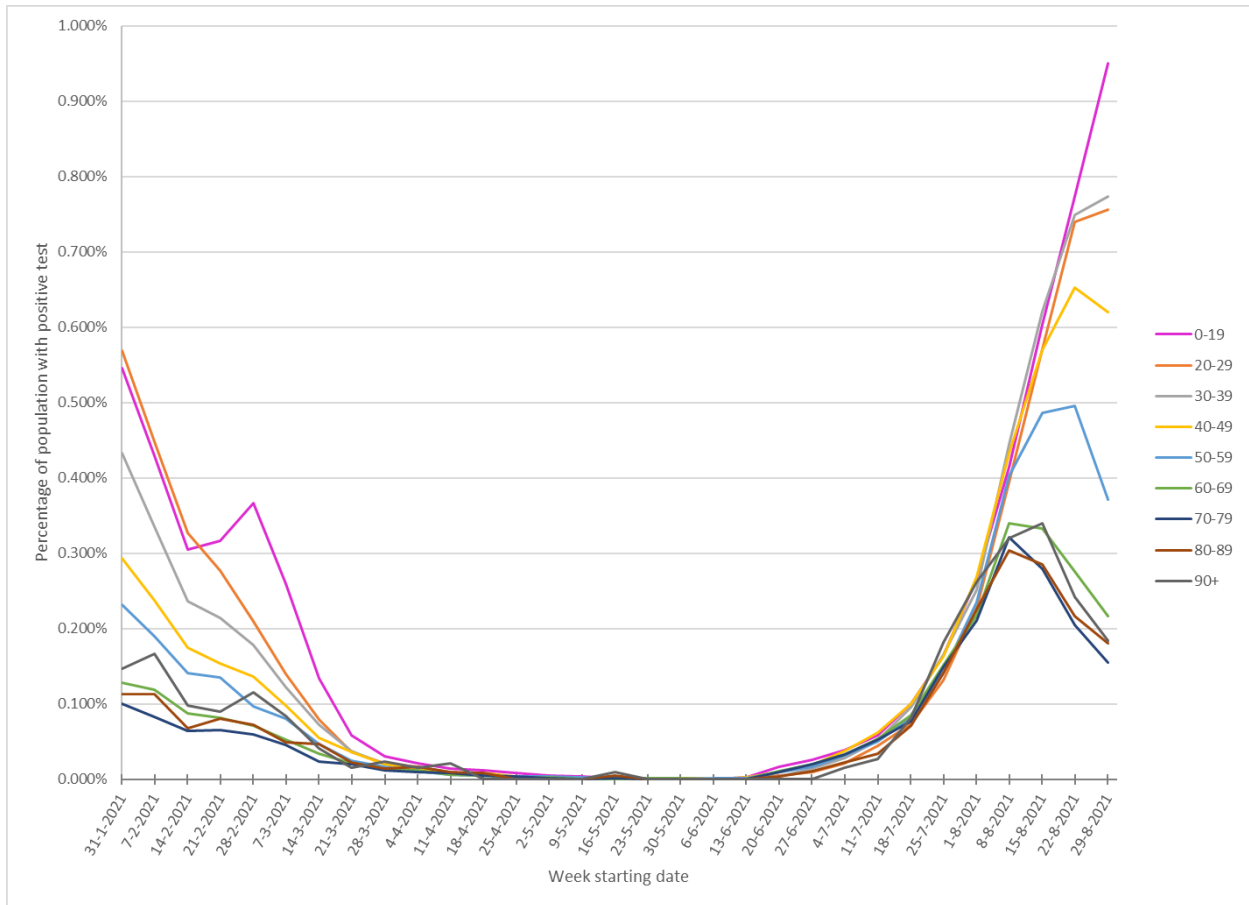
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Conflicts of interest

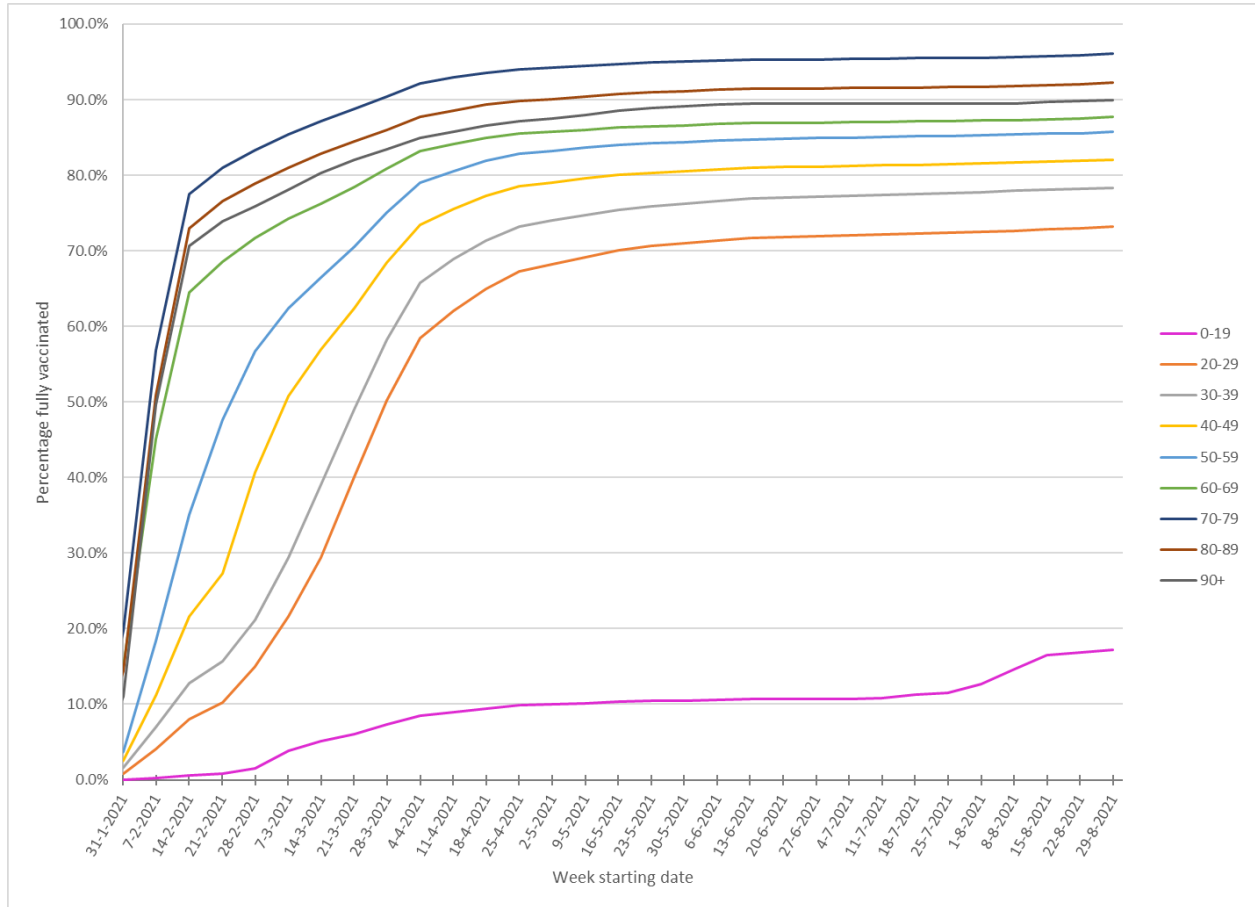
The author declares no conflicts of interest.

Figure 2. Percentage of the population of each age group with a positive test per week. In order to be consistent with the data in other figures, only the positive tests in fully vaccinated and unvaccinated individuals are used.

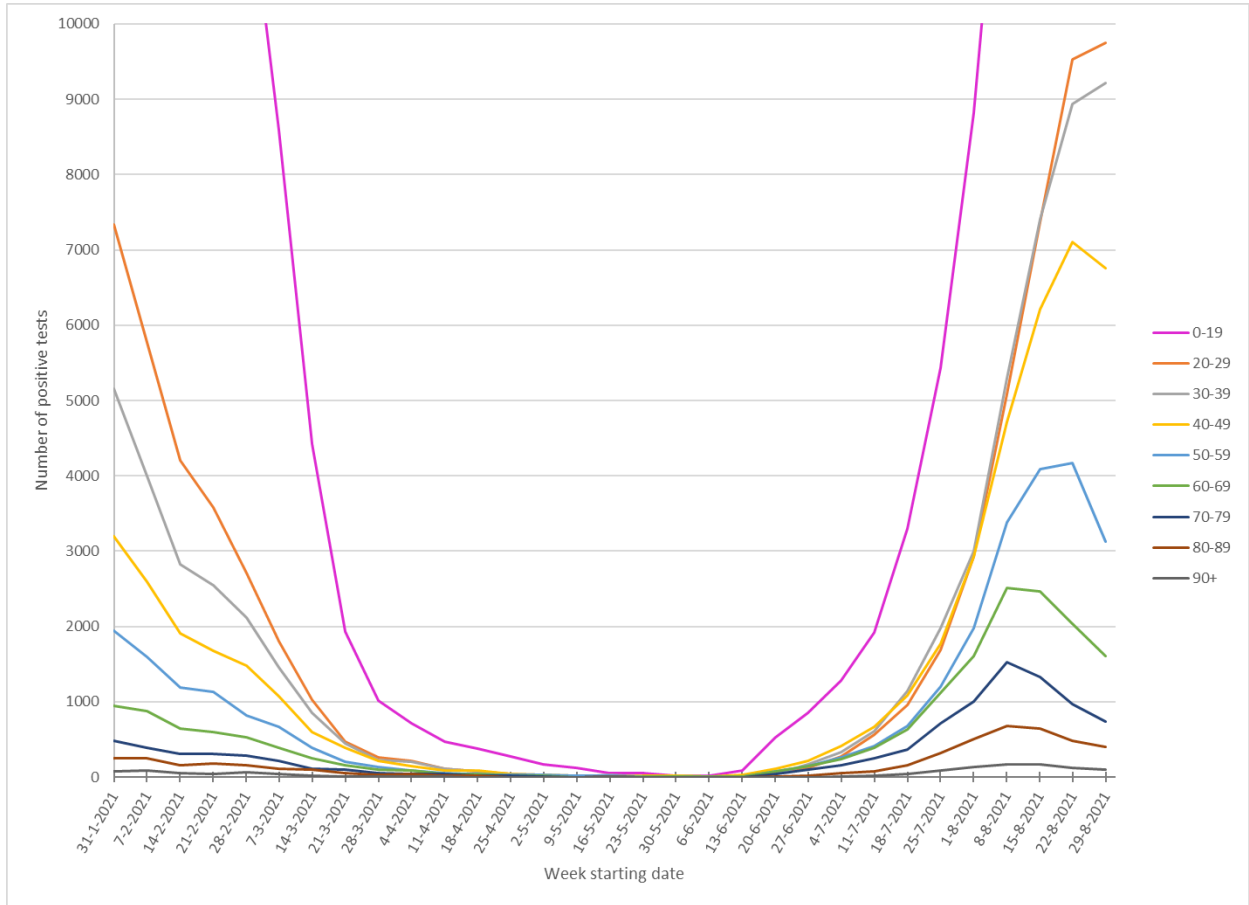


Supplementary data

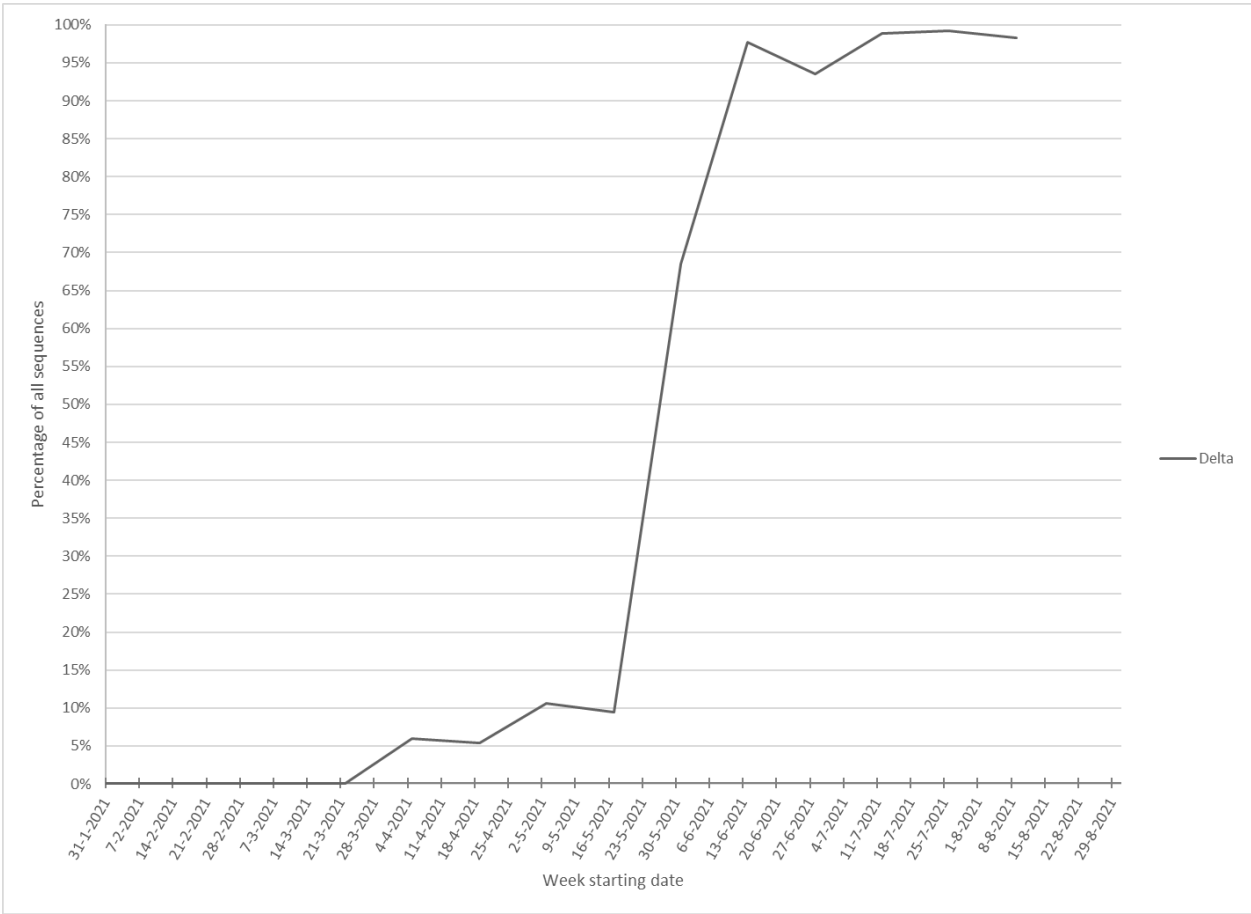
Supplementary data figure S1. Percentage of fully vaccinated people per age group per week.



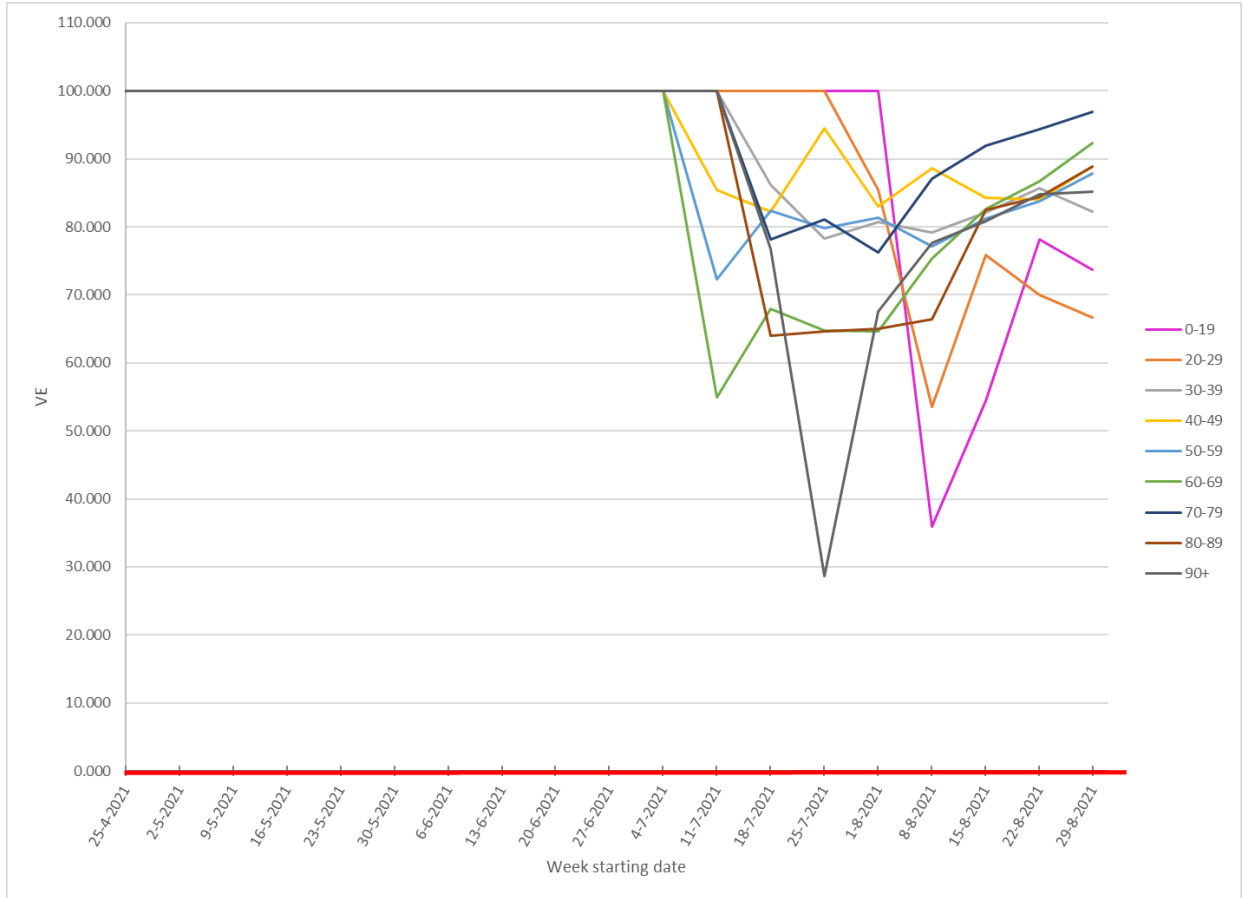
Supplementary data figure S2. Absolute number of positive tests in fully vaccinated and unvaccinated people per week per age group. In order to be consistent with the data in other figures, only the sums of positive tests in fully vaccinated and unvaccinated individuals are used.



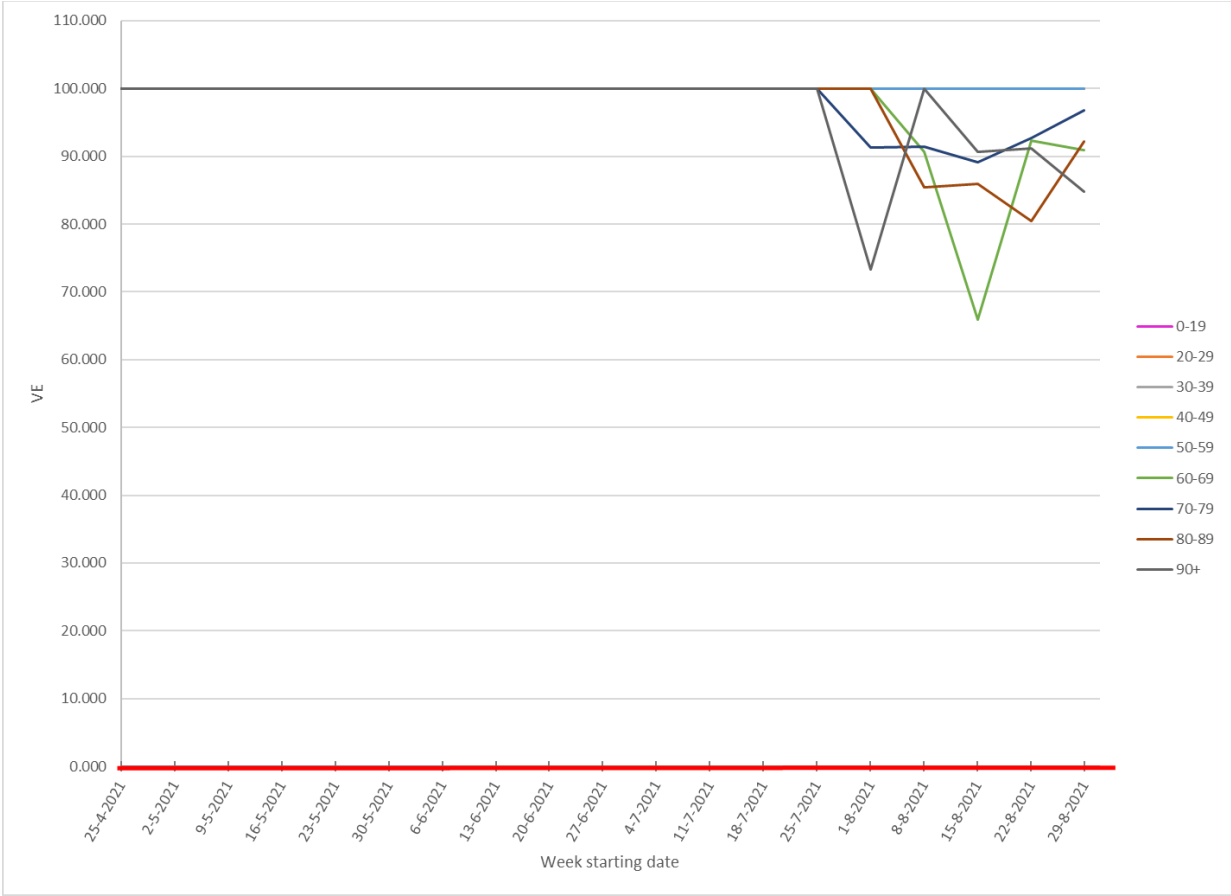
Supplementary figure S3. Percentage of all sequences that was identified as the Delta variant.



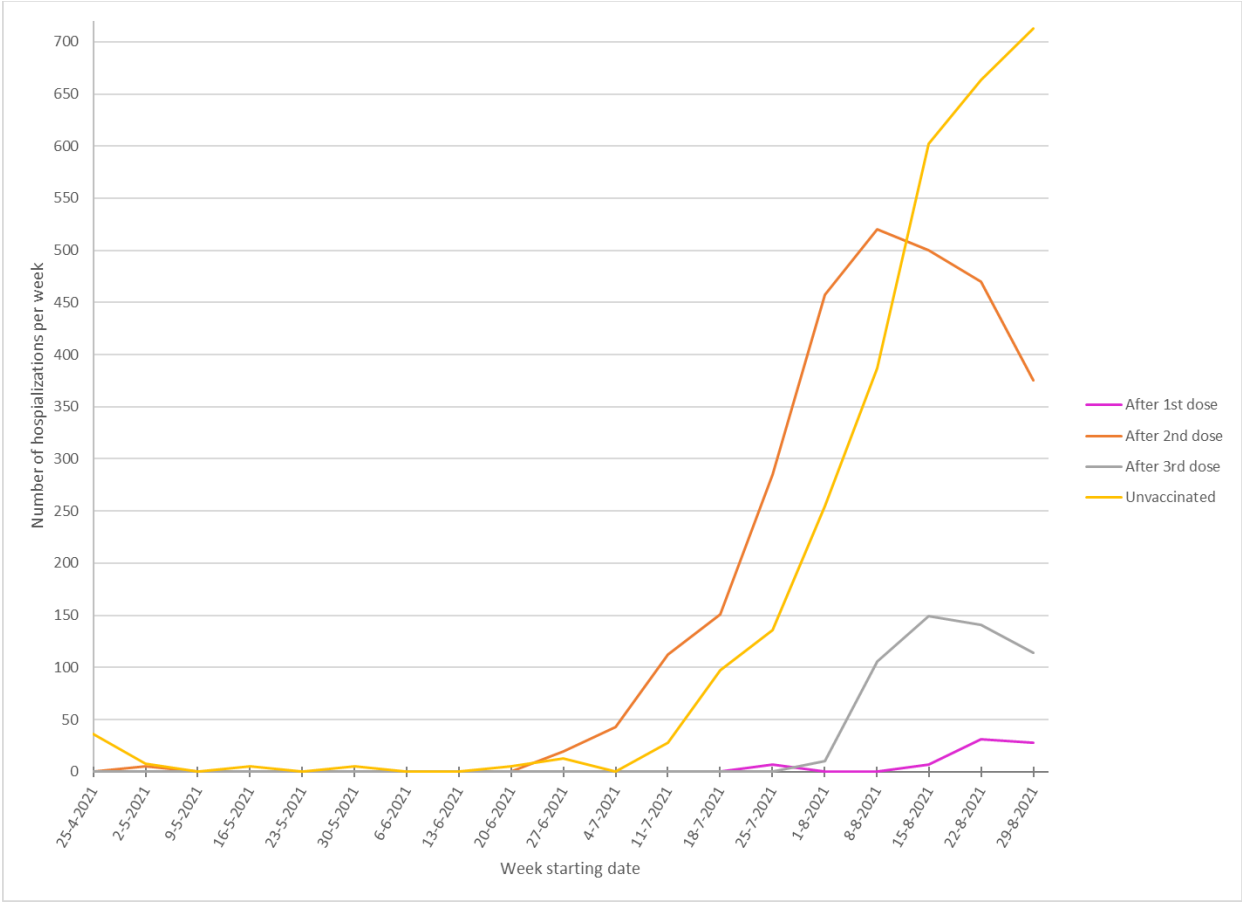
Supplementary figure S4. The VE for hospitalization per week per age group from end of April 2021 till end of August 2021. From the week of 25 April 2021 onward the full vaccination coverage has reached rather stable levels in all age groups (figure S1), which is why this is selected as starting week. VE: vaccine effectiveness.



Supplementary figure S5. The VE for death per week per age group from end of April 2021 till end of August 2021. From the week of 25 April 2021 onward the full vaccination coverage has reached rather stable levels in all age groups (figure S1), which is why this is selected as starting week. VE: vaccine effectiveness.



Supplementary figure S6. The total number of hospitalization per week per for people who have received no, 1, 2, or 3 doses from end of April 2021 till end of August 2021. From the week of 25 April 2021 onward the full vaccination coverage has reached rather stable levels in all age groups (figure S1), which is why this is selected as starting week.



Supplementary Table T1. Percentage of the population that received two doses. The values calculated using the data in the analysis consist of fully vaccinated people (i.e. ≥ 14 days after the second dose) and are based on the population size reported by the Israeli Central Bureau of Statistics for 2020. The values reported on the Israeli dashboard (<https://datadashboard.health.gov.il/COVID-19/general>) are calculated using population size data from April 2021. The age group 0-19 is omitted, because the dashboard only reports 12-15 and 16-19 and without the used population size this cannot be transformed to the percentage for 0-19.

	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90+
Analysis (%)	73.2	78.4	82.0	85.7	87.8	96.1	92.2	89.9
Dashboard (%)	72.6	78.3	81.4	83.5	87.5	87.5	87.2	79.7