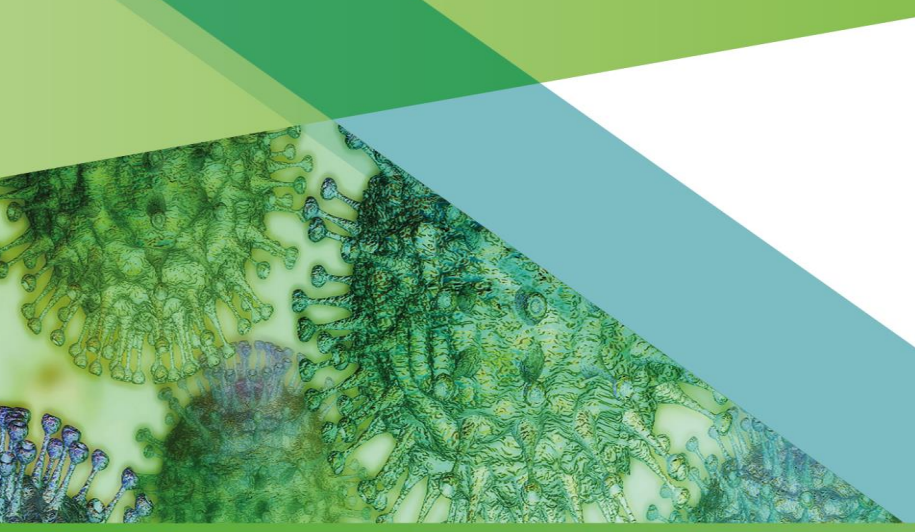

TECHNICAL REPORT

COVID-19 vaccine effectiveness in adolescents aged 12–17 years and interim public health considerations for administration of a booster dose

8 February 2022

Key messages

- The vaccination of adolescents was introduced during the summer of 2021, approximately six months after COVID-19 vaccines were introduced in EU/EEA countries. All EU/EEA countries now recommend COVID-19 vaccination of adolescents aged 12-17 years old, and of these, ten also recommend a booster dose for those under 18 years of age.
- To date, at the EU level, the administration of booster doses is currently exclusively authorised for individuals 18 years of age and older. The EMA Committee for Medicinal Products of Human Use (CHMP) is currently evaluating data on the use of booster doses in adolescents.
- As of week 4 (30 January 2022), the median uptake of the primary course of COVID-19 vaccine among adolescents aged 15-17 years old was 70.9% (range: 17.9-92.6%) and among 10-14 year-olds it was 34.8% (range: 3-63.8%) with broad heterogeneity across EU/EEA countries. More than half of adolescents aged 10 to 17 in the EU/EEA have not yet completed a primary course.
- SARS-CoV-2 notification rates of symptomatic disease in 12-17 year-olds have increased steadily since July 2021, largely mirroring the increased reporting rate observed in all age groups during the Delta and Omicron variant-dominated waves. However, a decrease in notification rates has been recently observed. The crude risk of hospitalisation, ICU admission and death remain very low for 12-17 year-olds.
- The studies available among adolescents mainly report vaccine effectiveness of the primary vaccination course against the Delta VOC and show a very high level of protection against infection, symptomatic disease, and severe disease.
- There is limited evidence available of waning of immunity following vaccination among adolescents. The available data suggest a waning of vaccine effectiveness against symptomatic infection five to six months following completion of the primary vaccination course, however no evidence of waning immunity against severe disease is currently available.
- There are currently limited data available on benefits and risks of a booster dose administered to adolescents who completed their primary vaccination course against COVID-19. Preliminary findings suggest an increase of vaccine effectiveness against documented SARS-CoV-2 infection in adolescents who received a booster compared to adolescents who have recently completed the primary vaccination course. However, no data are yet available on the duration of protection from a booster dose and on the additional effectiveness against severe disease of a booster dose in adolescents.
- Mathematical modelling suggests that the impact of administering a booster dose against COVID-19 to adolescents aged 12-17 years is a small reduction (1-3%) of the effective reproduction number (R(t)) in the whole population, varying according to the level of uptake of booster doses among adolescents.

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- When considering the possibility of administering a booster dose to adolescents who completed the primary course, data on the benefit-risk of a booster dose in this age group should be carefully reviewed as they become available. Additionally, consideration should be given to the epidemiological situation, the national priorities and objectives of the COVID-19 vaccination campaign, the status of the rollout of the COVID-19 vaccine and of additional doses in priority groups and in the general population, as well as vaccine equity and supply.
- At this stage, priority should still be given to completion of the primary series in the eligible population and to administering booster doses to priority groups, before considering giving booster doses to adolescents aged 12-17 years with no underlying conditions.

Scope of this document

Given the emerging evidence of waning immunity in adults following a two-dose schedule with authorised vaccines [1,2] and following requests from some Member States, the purpose of this document is to review the evidence of COVID-19 vaccine effectiveness and duration of immunity following vaccination in adolescents aged 12-17 years, and to outline interim public health considerations for the potential use of a booster dose in this group. It integrates a previous report on interim public health considerations for COVID-19 vaccination of adolescents 12-17 years which was published on 1 June 2021 [3].

This document does not focus on the effectiveness of additional doses of COVID-19 vaccine in severely immunocompromised adolescents, for whom additional doses should be considered as part of the primary vaccination schedule. Additionally, it does not provide a thorough review of safety data on COVID-19 vaccination in adolescents.

Providing policy recommendations or a thorough risk-benefit analysis of booster doses of COVID-19 vaccine in 12-17 years old individuals is also not within the scope of this report.

Target audience

The target audience for this report are National Immunisation Technical Advisory Groups (NITAGs) of the EU/EEA, public health authorities in EU/EEA Member States, and public health professionals.

Definitions

Primary vaccination course: dosage schedule provided according to initial authorisation in the EU/EEA [4].

Additional dose: this refers to any additional dose of currently authorised vaccines in the EU that are provided to complement the primary vaccination course for adolescents with severe immunocompromising conditions.

Booster dose: an additional dose of vaccine provided to adolescents in order to boost their immunity at an interval of at least three months after the primary vaccination course.

Current policies on vaccination of adolescents

Among COVID-19 vaccines authorised for use in the EU/EEA, only Comirnaty (for children above 5 years of age) and Spikevax (for children above 12 years of age) are currently licensed for use in children and adolescents, and the administration of booster doses is currently exclusively authorised for individuals 18 years of age and older [4].

All 30 EU/EEA countries are recommending primary vaccination against COVID-19 for 12-17-year-olds. Regarding the administration of a booster dose, most EU/EEA countries (19/30) are recommending booster doses to all adults 18 years and over and one country to priority groups including those aged 40 years and over. Ten countries are recommending boosters doses for adolescents below 18 years of age. Two countries are recommending booster doses to all those 16 years of age and over (Iceland and Ireland) and eight countries to all those 12 years and over (Austria, France, Germany, Hungary, Italy, Liechtenstein, Luxembourg and Romania) [5].

In the US, on 5 January 2022, the Centers for Disease Control and Prevention (CDC) endorsed the Advisory Committee on Immunization Practices' (ACIP) recommendations to also offer booster doses to those 12-15 years old, following on from the previous recommendation to offer them to those 16 years and above. CDC recommends that adolescents aged 12-17 years old should receive a booster dose five months after the completion of the primary vaccination series with Comirnaty. This decision was based on safety data following the administration of over 25 million vaccine doses in adolescents and data showing that booster doses strengthen the protection against the Omicron and other variants. Currently, Comirnaty is the only COVID-19 vaccine authorised and recommended for adolescents in the US [6].

Israel has recommended booster doses for everyone aged16 years of age and above since late August. In November, this was extended to also include those aged 12 to 15 years of age. Due to the spread of the Omicron variant, the Ministry of Health's Director General has issued a directive for the administration of a booster to be given within three months of the second dose, rather than five months afterwards, as was the protocol before [7].

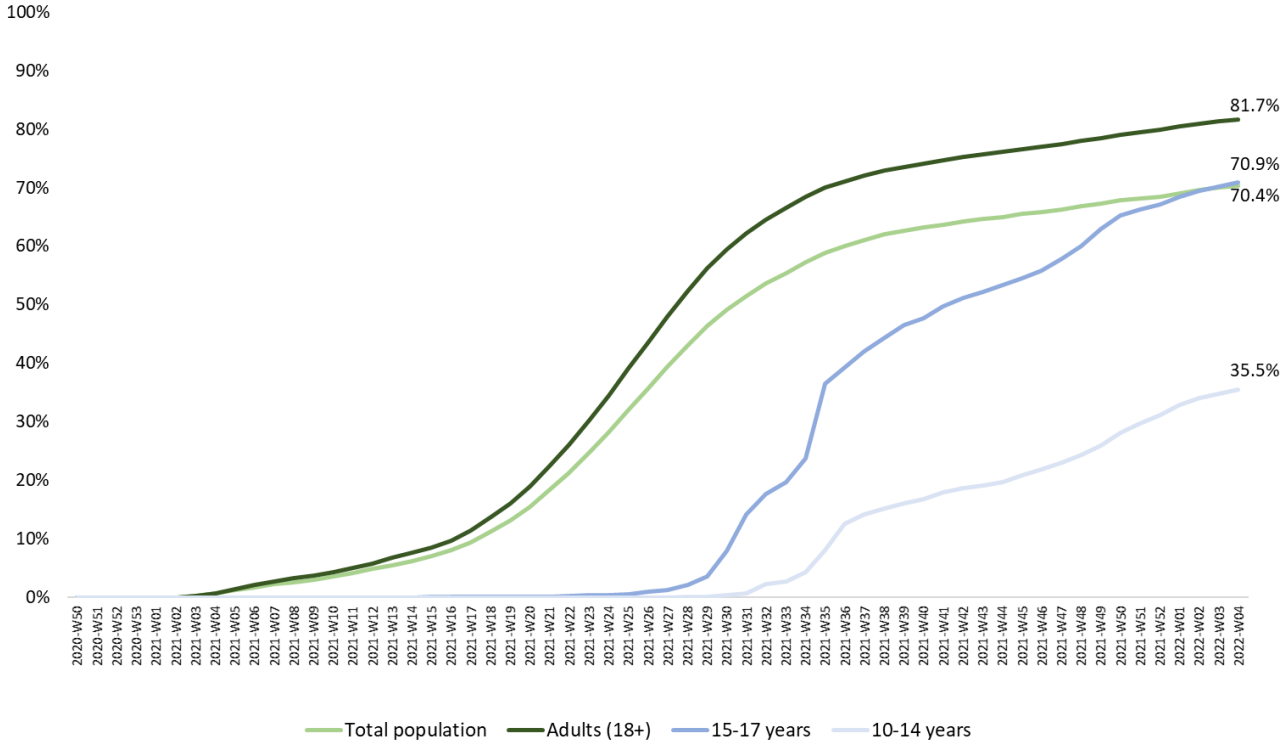
In the UK, the National Health Service has offered a booster dose of COVID-19 vaccine to all adolescents 16-17 years old since 17 January 2022. Previously, additional doses were only offered to 16-17 years old adolescents with risk factors for severe COVID-19 [8]. Switzerland also recommends booster doses to all adolescents 16-17 years of age [9].

In addition, on 21 January 2022, the World Health Organisation's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization issued an update of the roadmap for prioritising the use of COVID-19 vaccines, in which children and adolescents with comorbidities are identified as a medium priority-use population group for the administration of primary series and booster doses, while healthy children and adolescents are the lowest priority-use group because of their relatively low risk of severe disease, hospitalisation, and death. The decision to expand the administration of booster doses to lower priority-use groups should also consider the evidence of waning immunity and the vaccine coverage of higher priority-use groups first to optimise vaccination impact. For instance, countries with moderate-to-high rates of primary series coverage in higher priority-use groups should prioritise available resources to first achieve high booster dose coverage rates in higher priority-use groups before offering booster doses to lower priority-use groups [10].

Vaccine uptake in adolescents in the EU/EEA

As of week 4, 2022 (30 January 2022), the cumulative uptake of a complete COVID-19 primary vaccination course in the total population in the EU/EEA reached 70.4% (range: 28.9-84.4%) and 45.2% (range: 7.9-65.3%) for a dose in addition to the primary course (pooled data from 30 countries; this includes both booster doses and additional doses administered as extension of the primary course, for instance, in severely immunocompromised individuals). While the uptake of the primary course in the adult population (18 years and above) in the EU/EEA reached just over 80% (81.7%; range: 34.5-94.6%) and 54.8% (range: 9.6-82.6%) for an additional vaccine dose, the administration of the COVID-19 primary course in children and adolescents below 18 years of age started in most countries by the summer of 2021, according to a stepwise age-based prioritisation approach, and is currently still being scaled up. As of week 4, 2022, the median uptake of a primary vaccination course among adolescents aged 15-17 years was 70.9% (range: 17.9-92.6%; 17 countries reporting) and 35.5% among 10-14 year olds (range: 3-63.8%; 16 countries reporting) (Figure 1) [11].

Figure 1. Cumulative uptake of a primary course of COVID-19 vaccine in the total population, adults (18+ years) and adolescents in the EU/EEA as of week 04, 2022



Source: TESSy; data for total population and adults aged 18 and over reported by 30 countries as of week 04, 2022. The total population includes children for whom the vaccine is not yet indicated (e.g. below five years) or who may not be included in national target groups). For age groups of 10-14 and 15-17 years, data are available for 17 countries (missing Belgium, Bulgaria, Estonia, France, Germany, Hungary, Italy, Liechtenstein, Malta, the Netherlands, Norway, Romania, Slovenia; for Sweden only data for 15-17 year-olds are available).

Based on data reported by EU/EEA countries to TESSy, as of week 4, 2022, vaccine doses in addition to the primary course have already been administered to children and adolescents below 18 years in at least 26 countries, although in most of them (n=18) the uptake is still very low (<1%) and possibly related to the administration of additional doses as an extension of the primary series in children and adolescents with immune deficiency. Among countries with recommendations on the use of booster doses in adolescents, the median uptake is 26.7% (range: 21.3-31.6%) among 15-17 year-olds and 3.6% (range: 0.1-8.9%) among 10-14 year-olds, with few early adopting countries reaching higher levels among 15-17 year-olds, such as Iceland (31.6%) and Ireland (28%) (Table A1 in Appendix) [11].

Overall, progress in vaccine uptake remains unequal across EU/EEA countries. For more information on COVID-19 vaccine doses administered and vaccine uptake rates, please consult the ECDC Vaccine Tracker [11].

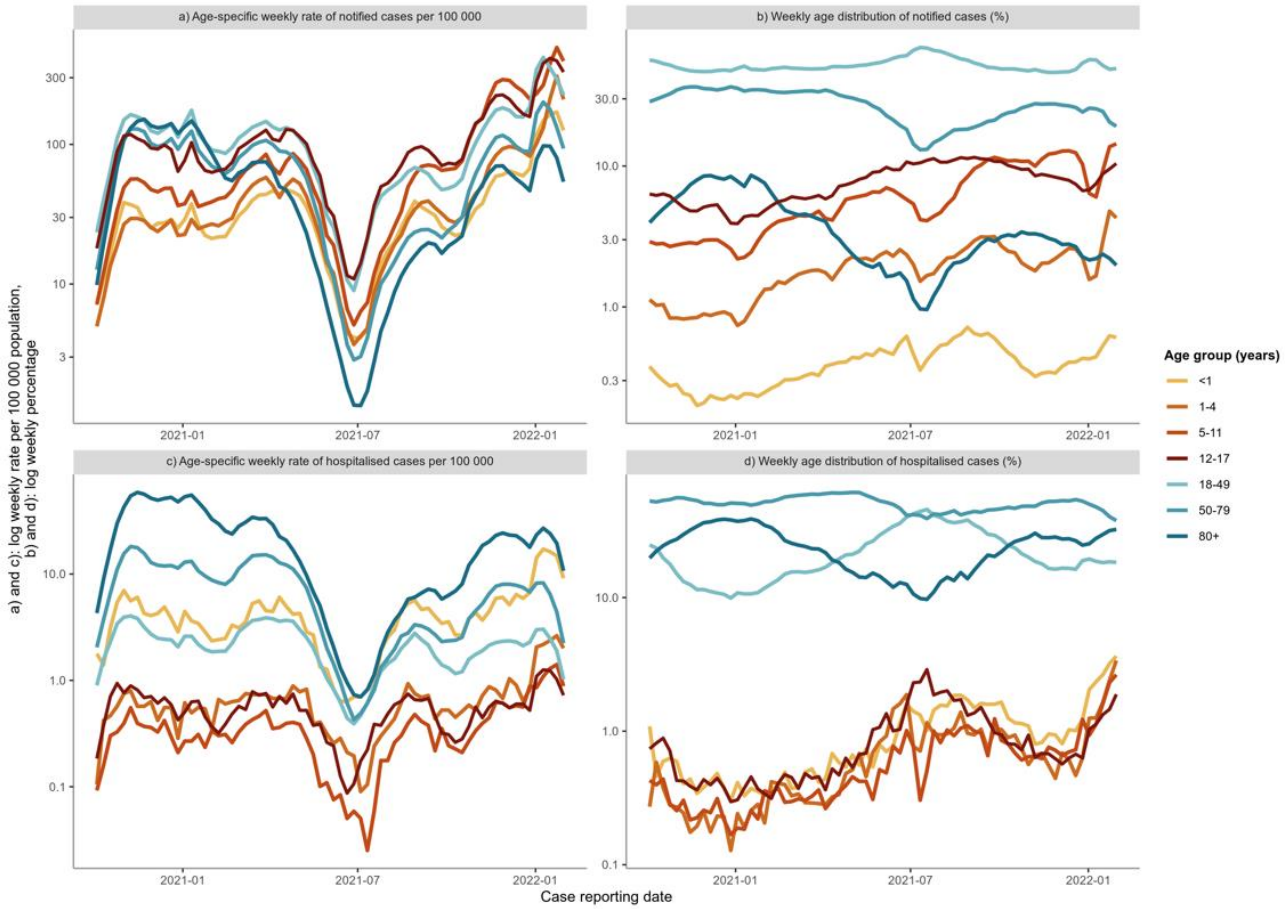
SARS-CoV-2 notification rates among adolescents

According to data reported to the European Surveillance System (TESSy) by EU/EA countries, SARS-CoV-2 notification rates among symptomatic individuals aged 12-17 years have increased steadily since July 2021, largely mirroring increased reporting rates observed in all age groups during the Delta and Omicron variant-dominated waves. However, a decrease has been observed in the early weeks of 2022, possibly due to changes in testing approaches, the Omicron peak, and/or reporting delay. Still, rates in the 12-17 year-old age group are currently amongst the highest of any age group in the EU/EEA (Figure 2). Notified cases in this age group constituted 10.4% of all cases notified in the EU/EEA in week 4 of 2022, while this group constitutes about 6% of the total population.

Concurrent with the increase in notification rates in symptomatic individuals aged 12-17 years during the second half of 2021, has been an increase in hospitalisation rates per 100 000 population in this age group. This too, has declined during the early weeks of 2022. Overall, hospitalisation rates remain low with about one hospitalisation per 100 000 population observed in week 4 of 2022. Analysis of cases reported for weeks 32 of 2020 through week 39 of 2021, so including the period before and after vaccination was implemented in in this age group, found that the overall crude risks of ICU admission and mortality were extremely low throughout the period in the 12-17 year old age group and that individuals with underlying comorbidities had significantly greater odds of hospitalisation (RR 9.3; 95% CI 5.9-14.5) and ICU admission (RR 24.8: 95% CI 4.5–137.1) than those without co-morbidities [12].

At present, it is not possible to differentiate notification rates or indicators for severe infection reported to TESSy by vaccination status for this age group, due to lack of complete data on all of the relevant variables.

Figure 2. Pooled weekly age-specific rates and distribution of symptomatic notified and hospitalised cases, 2020-week 40 to 2022-week 4



Note: Based on pooled case-based data from Austria, Cyprus, Finland, Germany, Ireland, Italy, Luxembourg, Malta, Slovakia and Sweden.

Vaccine effectiveness of COVID-19 primary vaccination course in adolescents

Evidence of vaccine effectiveness (VE) following primary vaccination in adolescents against asymptomatic and symptomatic infection due to the Delta variant is shown to be high in the short term, with evidence of waning from around five to six months following primary vaccination. VE of primary vaccination against severe outcomes including hospitalisation due to the Delta variant is high, with currently no evidence available on length of protection.

The studies of vaccine effectiveness in this age group are relatively few and the estimates may be subject to possible bias related to differential exposure of vaccinated and unvaccinated individuals in this age group. In addition, some study results are based on relatively small case numbers, and several of the studies are preprints that have not yet been peer-reviewed.

Vaccine effectiveness against infection and symptomatic infection

A test negative case control study from England (not yet peer-reviewed) with a focus on VE in adolescents estimated the VE against symptomatic infection due to the Delta VOC following one dose of Comirnaty in 16-17-year-olds at 14 days as 75.9% (95% CI, 74.3-77.4%) which declined gradually and plateaued at 37.4% (95% CI 30.8-43.3%) after eight to nine weeks. After dose two, VE increased and reached 94.6% (95%CI 92.8-95.9%) at two to nine weeks. In 12-15-year-olds, follow-up was limited to eight to nine weeks post dose one but followed a similar trajectory, with VE peaking at two weeks at 75.4% (95% CI, 73.9-76.9%) before declining to 46.8% (95% CI, 14.9-66.7%) by eight to nine weeks after one dose [13].

A peer-reviewed nationwide retrospective cohort study in adolescents aged 12-15 years from Israel found high short term VE following two doses of Comirnaty against COVID-19 infection with the Delta VOC. VE on days 8-28 post second dose was 91.5% (95% CI, 88.2-93.9%) [14].

Another peer-reviewed retrospective cohort study from Israel in adolescents aged 12-18 years also found high VE against infection with the Delta VOC following two doses of Comirnaty with VE of 90% (95% CI, 88 to 92%) seven to 21 days after the second dose and VE against symptomatic infection of 93% (95% CI, 88-97%) on days seven to 21 after the second dose [15]. A peer-reviewed retrospective cohort study from the United States, funded by Pfizer, estimated the effectiveness of two doses of Comirnaty among Delta cases in individuals 12 years and above. When stratified by age groups, it was found that VE against infection was highest in the 12-15 years age group; with VE of 91% (95% CI: 88–93%) compared to 73% (95% CI: 72-74%) in those ≥16 years of age. The level of effectiveness in 12-15 years olds was similar at one and two months after the second dose. The VE against hospitalisation was also investigated as well as the duration of the effectiveness over a longer time period but included very few cases in this age group [16].

Another peer-reviewed prospective cohort study from the United States estimated VE of two doses of Comirnaty against infection among a small sample size of adolescents, 12-17 years of age, between 25 July- 4 December 2021 while the Delta VOC was the predominant strain. The VE against infection was estimated at 92% (95% CI 79–97%) at 14+ days after primary vaccination with 19 weeks follow-up [17].

A recent study (published as preprint) assessed the neutralization activity of two-dose regimens Spikevax vaccination against Omicron VOC in adults, adolescents and children. The study found that a two-dose regimen of 100 µg Spikevax in adolescents and of 50 µg in children elicited neutralization responses against the Omicron variant that were reduced compared with the wildtype D614G, and numerically higher than those in adults [18].

Vaccine effectiveness against severe outcomes

A peer-reviewed case-control, test-negative study in the United States estimated the VE of two doses of Comirnaty against severe outcomes including hospitalisation, ICU admission, life-support intervention or death in adolescents aged 12-18 years when the Delta variant was predominant between July and October 2021. The study found the vaccine to be highly effective up to 90 days of follow up with an overall VE against hospitalisation of 94% (95% CI, 90-96%), 98% against ICU admission and 98% against receipt of life support. All seven deaths occurred in patients who were unvaccinated [19].

A peer-reviewed test-negative case control study from the United States estimated the VE among hospitalised patients aged 12-18 years with multisystem inflammatory syndrome in children (MIS-C), compared to hospitalised control patients during the Delta-dominant period. The VE against hospitalisation with MIS-C was estimated at 86% (95% CI 70-93%) at ≥14 days after completion of the primary vaccination course with Comirnaty, and 91% (95% CI 78-97%) at ≥28 days after vaccination [20].

A French study using electronic health record data estimated the risk of MIS-C among adolescents aged 12 to 18 years by COVID-19 vaccination status during September and October 2021. The results suggest that COVID-19 mRNA vaccination after one dose was associated with a lower incidence of MIS-C in adolescents. The hazard ration (HR) for MIS-C was 0.09 (95% CI, 0.04-0.21; P < .001) after the first vaccine dose compared with unvaccinated adolescents [21].

The test negative case control study from England (not yet peer-reviewed) with a focus on VE post one dose in adolescents against symptomatic infection, outlined in the VE against symptomatic infection section above, also estimated the VE against hospitalisation due to Delta variant in 16-17 year-olds at 14+ days post-dose one and found a VE of 85% (95% CI: 65-93%) [13].

Duration of protection from COVID-19 primary vaccination course in adolescents

A retrospective cohort study from Singapore (not yet peer-reviewed) estimated VE against COVID-19 infection and symptomatic infection in 12–18-year-olds following two doses of Comirnaty during the period of Delta variant dominance from 1 June till 20 November 2021. VE against all infections and against symptomatic infections over this period was 59% (95% CI: 55-63%) and 62% (95% CI: 57-66%), respectively, among adolescents vaccinated with two doses compared with unvaccinated adolescents. The study results also suggested gradual waning of immunity over four months post administration of the second dose and found that among those vaccinated with two doses, vaccine effectiveness against infection was 78% two weeks after administration of the second dose, and gradually declined to 54% after four months [22].

A study from Israel (not yet peer-reviewed) included a matched case-control analysis and a test-negative design analysis of VE of two doses of Comirnaty against all infections and symptomatic infections over time in adolescents aged 12-16 years. The study period was between 15 June-8 December 2021 while Delta was the dominant variant. In the matched case-control analysis, the VE against infection at 14-89 days following dose two was 85% (95% CI: 84-86%). This was reduced to 75% (95% CI: 71-79%) and 58% (95% CI: 52-64%) after 90-149 days and 150-180 days following receipt of the second dose, respectively. The results of the test-negative design showed a similar decline in VE. The VE against symptomatic infection in the 14-89 days following the second dose was 90% (95% CI: 89-91%) and subsequently decreased to 78% (95% CI: 73-82%) for days 90-149 and 65% (95% CI: 58-71%) for days 150-180 after the second dose [23].

In a recent prospective study from the US (not yet peer-reviewed), vaccine-induced serum IgG titres specific to the wildtype SARS-CoV-2 Spike protein, the wildtype receptor binding domain (RBD) and Omicron VOC RBD were measured by ELISA for 31 adolescent children (median age 13.9 years). Serum was collected at four time points: prior to vaccination, two to three weeks after a first dose of Comirnaty, two to four weeks after a second dose of Comirnaty, and again six months after the vaccination series was complete. Robust generation of anti-SARS-CoV-2 antibodies was seen following the second dose of Comirnaty, followed by a significant loss of antibody response after six months. While a few adolescents maintained high levels of anti-Spike or anti-RBD antibodies at six months, most children exhibited similar antibody levels to those detected after the first vaccine dose, or in the case of anti-Spike antibodies, pre-vaccine levels of antibodies [24]. Whilst this study quantitatively assessed serum antibody levels over time, it did not assess the virus-neutralising capability of sera, or the presence of SARS-CoV-2-specific memory B- and T-cells over time.

Evidence of benefits and risks of a booster dose of COVID-19 vaccine in adolescents

There are currently limited data on safety and effectiveness of an additional COVID-19 vaccine dose in adolescents. A cohort study from Israel (not yet peer-reviewed) investigated the effect of an additional (third) dose of Comirnaty in 16-18 years olds compared to individuals aged 12-14 who had recently completed their primary vaccination course with two doses of the same vaccine. The data were collected during the Delta-dominant period. The analysis showed that the additional dose provided a 3.7 (95% CI: 2.7-5.2%) fold increase in protection against documented infection compared to the primary vaccination course only [25]. The VE of the primary vaccination course calculated from the data in this study was estimated to be around 90% in both age groups, at 14-60 days after the second dose [26]. The VE of an additional dose was estimated at 92% (95% CI: 91-93%) when compared to unvaccinated and 73% (95% CI: 67-79%) when compared to individuals who completed the primary course [26].

No data are currently available about the effectiveness of booster doses to prevent severe COVID-19 or post-COVID-19 conditions in adolescents 12-17 years old.

According to safety data from the Centers for Disease Control and Prevention (CDC) in the United States, the most commonly reported adverse events in the age group 12-17 years old after primary vaccination series with Comirnaty were mild or moderate. Myocarditis was very rare and was reported as non-severe and more commonly occurring after dose two and in males [27]. This is consistent with safety data that have been reported by EMA [28,29]. Preliminary evidence from CDC of safety of an additional dose of Comirnaty in adolescents 16-17 years showed that most reported adverse events were not serious. Very rare cases of mild myocarditis were reported in lower rates than what was observed after dose 2 [27].

Estimated impact of a booster dose in adolescents on the effective reproduction number R_t at population level

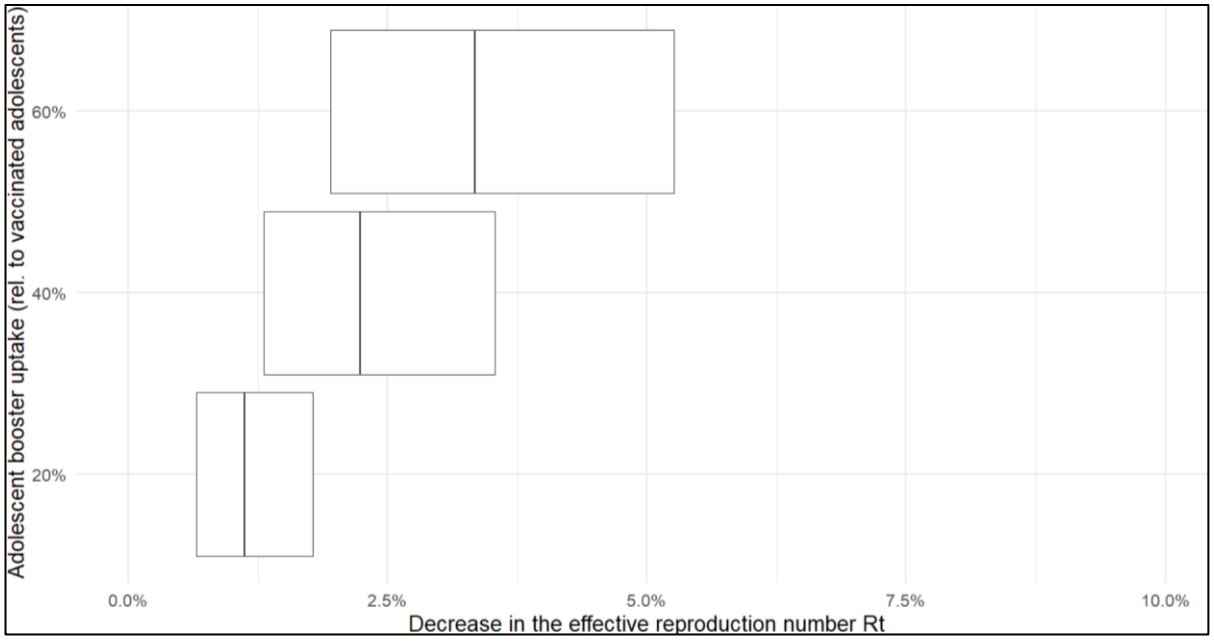
In addition to the direct burden of COVID-19 in adolescents, SARS-CoV-2 infections in adolescents contribute indirectly to the COVID-19 burden in the whole population due to onward transmissions to more vulnerable groups. Here, we quantify the effect of booster doses in adolescents (11-17 years old) on population spread of SARS-CoV-2 measured as the effective reproduction number R_t. Our approach is based on previously established methods [30-35].

Modelling the effect of booster doses is subject to substantial uncertainties regarding the characteristics of the Omicron variant (the level of immune evasion and the inherent transmissibility), the contacts among individuals in the population, the level of naturally-acquired immunity (through previous infections), the vaccination coverage, and vaccine efficacy. We take these uncertainties into account by considering plausible ranges of parameters. Therefore, our model yields as output a range for the decrease of the effective reproduction number R_t.

In brief, our model separates the EU/EEA population into four age groups: young children (0-4 years), older children (5-11 years), adolescents (12-17 years), and adults (18 years and older). Considering four separate age groups allows to account for not only age-specific primary vaccination course and booster uptakes, but also for heterogeneous contact rates (number of contacts per time) between individuals of different age groups. The contact rates vary strongly between the respective age groups and thus are crucial to the transmission of SARS-CoV-2. Estimates for the average contact rates between age groups in the EU/EEA are obtained from the CoMix study, which provides longitudinal contact data for several countries during different phases of the COVID-19 pandemic [34].

We evaluate the impact of providing booster doses to adolescents for three different scenarios: low booster uptake among adolescents (20% of previously vaccinated adolescents receive a booster), medium booster uptake among adolescents (40%), and high booster uptake among adolescents (60%). The three different scenarios are in the same order of magnitude as the booster uptake of the adults in the EU/EEA, which at the time of writing of this document equals 50.3% of the vaccinated adults. In the model, we assume Omicron as the only circulating VOC. Furthermore, the proportion of individuals that have had COVID-19 is considered to vary in the range 25-50%, and the proportion of vaccinated individuals (12 years and older) is considered to be in the range of 70% to 90%. We assume that, due to the effect of primary vaccination including waning, 6-20% of individuals in the whole population are protected against SARS-CoV-2 and thus cannot transmit onwards the infection if exposed. For individuals that received a booster, the protection against onward transmission is considered to vary in the range of 40-60%.

Figure 3. The expected impact of providing booster doses to adolescents on the SARS-CoV-2 transmission at population level, quantified by the relative decrease of the effective reproduction number R_t, for a high, medium, and low uptake of booster doses in the group of adolescents



The vertical bars correspond to the respective median estimate, and the boxes cover the 95% Confidence Interval (CI).

Figure 3 shows the estimated reduction of the effective reproduction number R_t due to providing booster doses to adolescents, which equals 1% (95% confidence interval [CI]: 1%-2%), 2% (95% CI: 1%-4%), and 3% (95% CI: 2%-5%) for the low, medium, and high booster uptake among adolescents, respectively. We emphasise that these reductions of the effective reproduction number R_t are only achieved in the long term, once the respective booster coverage among adolescents is reached. Prior to reaching the respective coverage, the reduction of the effective reproduction number R_t depends on the speed of booster roll-out among adolescents.

The modelling results indicate that providing booster doses to adolescents is unlikely to have a considerable effect on the population-level transmission of SARS-CoV-2. (These results are in line with the rather small, expected impact of vaccinating 5–11-year-old children on the population-level SARS-CoV-2 transmission) [35].

Additional considerations

The following potential objectives of vaccinating adolescents against COVID-19 were outlined in a previous report from ECDC [3]:

- Protecting adolescent health from COVID-19;
- Normalising life for adolescents;
- Reduction of viral circulation in the overall population.

These objectives would still be valid as the main rationale for administering a booster dose to adolescents who completed the primary vaccination series, with the presumption that the booster dose is needed to restore and maintain a long-lasting immunity. We emphasise that these objectives include preventing illness of adolescents and potential longer-term implications such as prevention of post-COVID-19 conditions, and potential additional objectives for providing booster doses to adolescents could include minimising the loss of days in education or the potential productivity loss from guardians needing to take time off work to care for the adolescents. Before considering booster doses against COVID-19 for adolescents 12-17 years old, a number of additional considerations need to be made.

Data on benefits and risks of boosting adolescents need to be carefully evaluated as they become available in the light of the current epidemiological situation and national priorities. Although specific evidence is currently not available, it is anticipated that the benefit-risk profile of a booster dose in adolescents may differ between those at increased risk of severe COVID-19 due to underlying medical conditions and those that are not, so special consideration should be given to the former.

The decision whether to administer booster doses to adolescents or not should also be taken in the context of the status, priorities and objectives of the national COVID-19 vaccination campaigns and the epidemiological situation. As in the initial phases of the COVID-19 vaccination rollout, the anticipated impact of booster doses is expected to be the highest if priority groups, who account for the highest burden of COVID-19 in the population, are protected first and with a high coverage. Given the vaccine-escape potential of Omicron VOC, adolescents with no risk factors for severe disease may also benefit, albeit to a much lower degree and for an unclear duration, from a booster dose. On the other hand, if the objective is to have an immediate, albeit modest, impact on community transmission, administration of booster doses in age groups where the highest transmission rates are expected could be considered. However, this may not be timely enough and may not last for more than a few months given the rapid waning of immunity against infection and onward transmission caused by the Omicron VOC because of its vaccine escape potential [36]. Another potential objective for boosting adolescents is to prevent post-COVID-19 conditions that according to some reports could be quite frequent in the younger age groups [37-39], however in the absence of clear data on their occurrence and of an agreed case definition, it is difficult to assess what the benefit from a booster would be in this respect.

Although likely to mirror data collected for young adults, adolescent-specific data on duration and quality of immunity following completion of the primary vaccination course are needed to define the optimal vaccination course for long-term protection against COVID-19. In the context of waning serum neutralising antibody titres, it is important to note that although lower titres may be observed in serum sampled three to six months after infection or vaccination, this may be compensated by the persistence of virus-specific, long-lived memory B cells that are able to rapidly expand during subsequent infection to generate higher neutralising antibody titres [40-42]. Furthermore, non-neutralising antibody and memory T cell responses targeting conserved SARS-CoV-2 domains are likely to also contribute to protection from severe disease [43-45].

Finally, equity across all groups in the population should be ensured so that no vulnerable group is left behind due to challenges in reaching them or with vaccine acceptance. Global equity and access to COVID-19 vaccines for all countries that have very low levels of vaccination coverage is always a factor to consider when offering additional vaccine doses to population groups at lower risk of severe COVID-19.

Conclusions

Available studies looking at COVID-19 vaccine effectiveness of primary vaccination course against infection, symptomatic disease and severe disease due to the Delta VOC show a very high level of protection in adolescents 12-17 years. The limited evidence available concerning duration of protection against the Delta VOC suggest waning of vaccine effectiveness against symptomatic infection five to six months after completion of the primary vaccination course. No evidence of vaccine effectiveness against Omicron VOC in adolescents and on duration of protection against severe disease after the primary vaccination course in adolescents was available at time of drafting this report.

Preliminary data on vaccine effectiveness of a booster dose in adolescents suggest an increase in protection against documented SARS-CoV-2 infection compared to the primary vaccination course, however there is currently no information on duration of protection nor on additional effectiveness against severe disease. According to our mathematical modelling estimates, the indirect benefit for the whole population of vaccinating adolescents, in terms of reduction of the effective reproduction number (Rt), is estimated to be modest. Based on the current limited information on benefit-risk of booster doses in adolescents and the estimated modest additional impact on the effective reproduction number, at this stage priority should continue to be given to the completion of primary vaccination course for all the eligible population and to the provision of additional doses of vaccine to risk and priority groups according to the national recommendations. As more benefit-risk data on booster dose in adolescents becomes available, further considerations should include the local epidemiological situation, the national priorities and objectives of the vaccination campaign, the status of the rollout and uptake of the COVID-19 vaccine, and vaccine equity and supply.

Knowledge gaps and limitations

- Safety data on booster doses in adolescents 12-17 years are currently under review by the regulatory authorities.
- Real-life information about duration of protection after completion of primary vaccination course among adolescents is currently limited.
- Data on vaccine effectiveness against transmission, infection and severe outcomes caused by the of the Omicron VOC are currently limited and missing for adolescents aged 12-17 years.
- There are uncertainties regarding estimates of severity or duration (hospitalisation, deaths, short- and long-time conditions) of disease caused by the Omicron VOC, including longer term follow up, in this age group.
- Vaccine effectiveness data for adolescents at increased risk of severe COVID-19 (e.g. immunocompromised adolescents) are currently not available.
- In the modelling analysis of the impact of administrating an additional dose to adolescents on viral transmission, variations in social behaviour according to spatial/geographical heterogeneities, fluctuations of contacts over time, heterogeneities within age groups, age-specific transmissibility and risk of infection could not be quantified and accounted for.
- Accurate and up-to-date information on immunity from natural infection in unvaccinated adolescents is missing and is expected to change rapidly with the current high case notification rates.
- The possible emergence of new variants of concern will introduce new uncertainties.

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Disclaimer

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Annex

Table A1. Number of additional vaccine doses and uptake of doses in children and adolescents below 18 years of age in EU/EEA countries that recommend their use under the age of 18 as of week 04, 2022

	N. additional doses			Uptake additional dose		
Country	**<18 years**	**15-17 years**	**10-14 years**	**<18 years**	**15-17 years**	**10-14 years**
Austria[1]	94 542	66 076	28 384	6.1%	25.5%	6.7%
France[1]	426 290	-	-	2.9%		
Hungary[1]	39 856	-	-	2.3%		
Iceland[2]	4 176	4 159	17	5.1%	31.6%	0.1%
Ireland[2]	56 769	54 723	1979	4.7%	28.0%	0.6%
Italy[2]	638 838	-	-	6.8%		
Luxembourg[1]	7 099	4 151	2 948	5.9%	21.3%	8.9%
Romania[1]	9 239	-	-	0.3%		

Source: TESSy; data reported by 8 countries as of week 04, 2022.

Note: "Additional vaccine doses" refer to doses administered in addition to the primary course, being them an extension of the primary course (e.g. in immunocompromised individuals) or a booster dose to individuals who completed the primary course.

[1]*Recommending booster doses to individuals aged 12 years and above*

[2]*Recommending booster doses to individuals aged 16 years and above*