

COMMENTARY

COVID-19 vaccination in children and university students

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Abstract

Strategies for the use of COVID-19 vaccines in children and young adults (in particular university students) are hotly debated and important to optimize. As of late August 2021, recommendations on the use of these vaccines in children vary across different countries. Recommendations are more uniform for vaccines in young adults, but vaccination uptake in this age group shows a large range across countries. Mandates for vaccination of university students are a particularly debated topic with many campuses endorsing mandates in the USA in contrast to European countries, at least as of August 2021. The commentary discusses the potential indirect impact of vaccination of youth on the COVID-19 burden of disease for other age groups and societal functioning at large, estimates of direct impact on reducing fatalities and nonlethal COVID-19-related events in youth, estimates of potential lethal and nonlethal adverse events from vaccines and differential considerations that may exist in the USA, European countries and nonhigh-income countries. Decision-making for deploying COVID-19 vaccines in young people is subject to residual uncertainty on the future course of the pandemic and potential evolution towards endemicity. Rational recommendations would also benefit from better understanding of the clinical and sociodemographic features of COVID-19 risk in young populations and from dissecting the role of re-infections and durability of natural vs. vaccine-induced immunity.

KEYWORDS

children, COVID-19, university students, vaccination

1 | INTRODUCTION

Vaccines have been a major development in the fight against the COVID-19 pandemic. One of the most hotly debated issues surrounding their use is the vaccination of children and of young adults, in particular university students. Issues of health, education and societal well-being at large are at stake. Evidence,

recommendations and vaccination practices have evolved rapidly in a shifting sand environment with substantial variability across different countries. This commentary aims to provide a critical assessment of the situation with focus on what is known on the benefits and risks of COVID-19 vaccination in these populations and what are still remaining uncertainties as of late August 2021.

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2 | AUTHORIZATION, RECOMMENDATIONS AND VACCINE UPTAKE TO-DATE

Initial authorizations granted for COVID-19 vaccines focussed on adults, except for the Pfizer mRNA vaccine that also included adolescents of age 16 and older. Subsequently, the Pfizer vaccine received emergency use authorization for ages 12 and above in early April 2021 in the USA and conditional marketing authorization in late May 2021 in the European Union. The Moderna mRNA vaccine was similarly authorized in the European Union in July 2021 for children 12 years and older. These authorizations were based on favourable short-term trial results.

Recommendations have not been similar across countries, especially for children. An illustrative comparison of USA, UK and Sweden shows their divergent strategies. The American Academy of Pediatrics¹ and Centers for Disease Control and Prevention² have recommended vaccination for children older than 12 years since May 2021. As of late August 2021, 13% of children younger than 18 in the United States have been fully vaccinated. Conversely, the UK delayed deciding on whether to vaccinate children. On 19 July 2021, the UK Joint Committee on Vaccination and Immunisation recommended³ vaccinating children aged 12 to 15 years only if they are at higher risk due to severe neurodisability, Down syndrome, severely weakened immune system, or profound and multiple learning difficulties. An indirect protection strategy was also adopted to recommend immunizing children 12 to 17 years old if they live with older people who have a suppressed immune system. Even more cautious, Sweden started vaccination of adolescents 16–18 years old much later and has not started vaccinations in children under 16 as of late August 2021.

Vaccinations for young adults had already begun in early 2021, and as of late August 2021, there is more similarity across countries in their recommendations for these age groups. Nevertheless, in real practice, the proportion of young adults vaccinated varies tremendously across countries, reflecting the compounded differences in vaccine availability, efficiency of vaccination programmes and vaccine hesitancy. As of late August 2021, full vaccination has been achieved^{4,5} for 65% in the 18–24 years old age stratum in Belgium vs. 50% in Italy, 47% in the USA, 36% in Portugal, 16% in Sweden, 8% in Bulgaria and 4% in Peru. There are many low-income and middle-income countries with extremely low vaccination rates not only among young adults but even among the elderly.

The Pfizer vaccine was fully licenced for ages 16 and above in the USA on 23 August 2021; other vaccine manufacturers have submitted or may submit applications for

full licencing in the near future. Moreover, clinical trials are ongoing for children younger than 12 years old.

3 | MANDATES FOR UNIVERSITY STUDENTS

A substantial number of US colleges (773 campuses as of August 24, 2021) have issued vaccination requirements for at least some students and/or employees, but details, target groups and stringency of rules vary remarkably.⁶ In the UK, on 16 August 2021, Hartpury University and College was the first to require mandatory vaccination for students living on-site and for those participating in sports activities. As of August 2021, universities in European countries are generally not using mandates,⁷ but typically they encourage vaccination of students without mandating it.

The ethics and legality issues of vaccine mandates (including requirements from private institutions and public schooling mandates) have attracted thoughtful debate even before COVID-19 vaccines became available⁸ and their discussion is beyond the scope of this Commentary. Politicization and legal controversies have unfortunately created polarization surrounding this topic in the USA. Tension may mount also in other countries, especially if perpetuated epidemic activity continues to disrupt the re-establishment of a regular educational experience after a year and a half of devastating disruption of all educational levels. It is extremely important to ensure that schools and universities reopen (and remain open) for in-person teaching and resumption of many other activities.

4 | CLAIMED INDIRECT BENEFITS AND HARMS OF VACCINATING YOUNG AGE STRATA

Given that children and young adults carry only a very small portion of the COVID-19 serious disease burden at the population level, much of the heated debate about vaccination recommendations and strategies on these age groups is fought about indirect benefits to other age groups and society at large.

For example, it is often anticipated that vaccinating young populations may help families return to normal activities and may reduce outbreaks and deaths among older individuals who might otherwise be infected by younger people. Young people can be major drivers of active epidemic waves (in terms of their share in numbers of documented cases), especially with the delta variant that is dominant in many countries as of this writing.

However, opposite arguments also exist, for example that vaccinating the youngest age strata may shift infection to higher ages with higher case fatality⁹ especially as many elderly people in many countries are still not vaccinated and some vaccinated elderly have insufficient immune responses. Vaccinated people may still transmit the virus; given that vaccination makes infections milder/asymptomatic and people markedly increase exposures after vaccination (a risk compensation behaviour),¹⁰ vulnerable people may be exposed more frequently to vaccinated infected youth who are unaware of their infection.

These potential indirect effects are important to keep in mind. However, from an ethical perspective, the benefit-risk ratio in young people themselves should probably be a prime consideration.

5 | DEATH TOLL TO-DATE AND POTENTIAL FOR LIVES SAVED WITH VACCINATION

The number of potential deaths that can be averted by vaccination in young age strata for the coming year is uncertain, especially with the emergence of the delta variant and large uncertainty regarding any future viral evolution. A sense of the potential death toll can be gleaned from COVID-19 deaths that have already cumulatively occurred in these age strata over 2 annual seasons.

Table 1 provides relevant data on reported COVID-19 fatalities for the USA and for 6 European countries. USA have had higher rates of COVID-19 mortality in youth (5 and 51 per million for 0- to 17-year-old and 18- to 29-year-old strata respectively) compared with these other high-income countries. Differences are several-fold compared with England and Wales, Italy, Portugal, Sweden and Switzerland that otherwise had also many documented cases and similar mortality rates as the United States for their older populations. Estimated COVID-19 mortality rates for youth appear to be 6–10 times lower in the Netherlands vs. the US. In countries with low numbers of COVID-19 fatalities in children and young adults, vaccinating youth makes a less convincing case.

The 18- to 29-year-old stratum is particularly heterogeneous in COVID-19 death risk, with 10-fold or more difference in 18-year-old vs. 29-year-old students. Average college student age in the USA is 26 years, but many first-year students are 18 years old and other students (such as those in graduate programmes) are older than 29 years.

In contrast to USA and high-income European countries, less wealthy countries (such as India and Indonesia)

TABLE 1 Estimated COVID-19 mortality rates in the US and selected European countries^b

Country	US ^a (8/25/2021)	England and Wales (8/13/2021)	Italy (8/18/2021)	Portugal (8/25/2021)	Sweden (8/26/2021)	Switzerland (8/23/2021)	the Netherlands (8/3/2021)
Number of COVID-19 deaths							
Children 0–19 years ^c	385	46	31	5	15	3	3
Young adults 20–29 years	2761	210	70	13	22	3	12
Adults >29 years	620,839	140,833	127,604	17,651	14,645	10,449	17,817
COVID-19 mortality per million population							
Children 0–19 years ^c	5	3	3	3	4	2	0.8
Young adults 20–29 years	51	27	11	12	17	3	5
Adults >29 years	3029	3762	2947	2441	2220	1802	1578

^aPresented data for the USA pertain to 0–17 years for children and 18–29 years for young adults.

^bData on COVID-19 mortality overall and per age group are derived from the Centers for Disease Control and Prevention for the USA (https://www.cdc.gov/nchs/nyssr/nyssr/covid_weekly/index.htm) and the latest national situational reports in the other countries as provided in <https://dc-covid.site.ined.fr/en/> (last searched on 31 August 2021; the date of the data for each country in given next to the country name). Mortality rates per million are calculated using population estimates for the respective age strata (derived from populationpyramid.net for the USA and from <https://dc-covid.site.ined.fr/en/> for the other countries). Only select high-income countries are shown in the Table.

^cMortality risk may vary substantially within the group of children according to age. For the USA (where a large enough number of deaths in children have been recorded to allow meaningful examination of more granular age strata), there have been 94 COVID-19 deaths among infants <1 year old, 47 deaths among children 1–4 years old and 131 deaths among children 5–14 years old, which correspond to COVID-19 mortality of 25, 3 and 3 per million population respectively.

apparently have a higher share of COVID-19 deaths among the young given their much younger population pyramids. However, most of these countries have been slow vaccinating even older, vulnerable populations who are at markedly higher risk.

According to the COVerAGE database,¹¹ as of May 2021, data from 79 countries accounting for 2.7 million COVID-19 deaths (69% of all documented global COVID-19 deaths) show that over 8700 (0.3%) of these deaths are in children and adolescents under 20 years of age (40% in children 0–9 years old and 60% in adolescents 10–19 years old). For illustrative comparative purposes, estimated annual fatalities for seasonal influenza preceding the COVID-19 pandemic included 9243 to 105,690 deaths of children younger than 5 years (from data limited to 92 countries)¹² with much of that burden driven by nonhigh-income countries and unvaccinated children.

In extrapolating past COVID-19 experience to future fatality projections, it should be acknowledged that many children and young adults have already been infected¹³ and many may thus have acquired natural immunity. Moreover, future infection fatality rate may decrease with better protection of vulnerable children, more effective treatments and avoidance of harmful treatments (eg, improper mechanical ventilation strategies). During 2021 in many countries, COVID-19 deaths' demographics shifted modestly to younger age groups.¹⁴ However, this may reflect mostly the better protection of the elderly given their higher vaccination rates rather than increasing propensity of new dominant viral strains to harm younger hosts. A typical transition from a pandemic phase to endemicity would indeed be characterized by circulation of the virus mostly among the young with limited total fatalities.

6 | LETHAL ADVERSE EVENTS FROM VACCINES

Although rare, potentially lethal thrombosis/haemorrhage events have been associated with adenoviral-vector vaccines (death risk 1:43,000 in Norway for the AstraZeneca vaccine, <1:1 million in the United States for the Johnson & Johnson vaccine).^{15,16} Risk of COVID-19-related death has been reported to be approximately 1.5-fold higher in males, and deaths with adenoviral-vector vaccines have occurred mostly among young women,¹⁵ making vaccination risk-benefit ratios more unfavourable in young females. To date, adenoviral-vector vaccines have not been authorized for use in children; in several countries, they were used in young adults but currently they tend to be disfavoured in these

age groups. For mRNA vaccines, lethal myocarditis is an extremely rare occurrence. Other lethal events with rates of 1 per 2 million vaccine recipients can be excluded with 95% certainty only after not occurring in 7,700,000 vaccinated children. Under-reporting during pharmacovigilance may decrease further the ability to detect exceptionally rare fatal events.

7 | NONFATAL EVENTS: BENEFITS AND RISKS

Given the extremely low rates of COVID-19 fatalities and of vaccine fatalities in young age groups, nonfatal outcomes matter a lot in decision-making. Gargano et al.¹⁷ estimate that per million second doses of mRNA COVID-19 vaccine administered to males aged 12–29 years, 11,000 COVID-19 cases, 560 hospitalizations, 138 ICU admissions and six deaths could be prevented, compared with 39–47 myocarditis cases after COVID-19 vaccination. For females aged 12–29 years, the respective estimates quoted (per million) are 12,500 COVID-19 cases, 922 hospitalizations, 73 ICU admissions and 6 COVID-19 deaths vs. 4–5 myocarditis cases. Rosenbaum et al.¹⁸ also provide tables with estimates of benefits and risks for various adverse events, including myocarditis, thrombosis-thrombocytopenia syndrome and Guillain-Barre syndrome.

All these comparative estimates would strongly tip the balance in favour of vaccination. However, it should be cautioned that estimates of adverse events are based largely on passive surveillance and it is well-known that passive surveillance can suffer from major under-reporting, even more so for nonfatal events. For example, the risk of anaphylaxis was 20- to 100-fold higher in a study with active data collection (2.47 per 10,000) vs. the passive pharmacovigilance data (0.025–0.11 per 10,000).¹⁹ Conversely, benefits are projected based on past data from the USA where reported fatalities were much higher in children and young adults than in most other high-income countries (as discussed above) and where over-attribution of paediatric deaths²⁰ to COVID-19 and overcounting of paediatric hospitalizations probably has existed.²¹ Modelling projections of benefits are occasionally helpful, but also precarious.

Furthermore, short-lived, mild adverse events are very common with COVID-19 vaccines and may temporarily affect quality of life. Moreover, the frequency and severity of long-term sequelae of COVID-19 are unknown²² and create added uncertainty. Similarly, any long-term adverse events from vaccines are also unknown and their evaluation requires careful, unbiased post-authorization and post-licensure studies.^{23,24}

8 | SOCIODEMOGRAPHIC FEATURES AND RISK STRATIFICATION

Besides age—that has a major impact of risk stratification both for COVID-19 risks that can be averted from vaccination and for some of the known adverse events of vaccination—other clinical and socioeconomic factors may also markedly affect risk-benefit ratios. Most COVID-19 hospitalizations and deaths occur in people with major comorbidities²⁵; this applies also to young age strata. For children and young adults without comorbidities, risk of severe COVID-19 disease outcomes is likely far lower than the overall risk in these age groups. Moreover, COVID-19 is a disease of inequality, with worse COVID-19-related health care (eg, access to testing), and much higher burden of disease and severe outcomes in disadvantaged populations, lower socioeconomic strata and specific racial groups. However, the paediatric literature on these inequalities is sparse^{26–28} compared with studies in adults and elderly people. Detailed granular information on the sociodemographic profile of COVID-19 severe disease and deaths in children and young adults needs to be collected and analysed across different countries with varying profiles for social determinants of disease. Such evidence may afford better risk stratification to rationally design vaccination and/or other intervention strategies targeted specifically towards subsets of high-risk individuals and settings—concurrently perhaps sparing unnecessary interventions among those at negligible risk.

9 | UNCERTAINTY FOR FUTURE EPIDEMIC ACTIVITY AND EXISTING IMMUNITY

The greatest uncertainty surrounding vaccination strategies pertains to the nature, activity and lethality of COVID-19 epidemic waves during the period when vaccination is supposed to provide protection. The relative strength and durability of protection after natural infection vs. vaccination is still unclear, and natural vs. acquired protection may vary for different emerging variants of concern. The role of re-infections^{29,30} and the impact of boosting natural immunity by vaccine³¹ need better study focussing on hard clinical outcomes (hospitalization, ICU admission and deaths). As of this writing, the delta variant is widely circulating in many countries. It is unknown whether other variants may become dominant in the future. Major new waves may appear soon if immunity wanes rapidly or escape viral variants become

dominant bypassing existing natural or even current vaccine immunity.

Preliminary data from Israel released as preprint on 25 August 2021 suggested that those who had no previously documented infection and received two doses of the Pfizer vaccine had a much higher risk of breakthrough infection, symptomatic disease and hospitalization than those who had documented previous infection.³² If these results are validated, they suggest that natural immunity confers much stronger and more durable protection than two doses of the specific vaccine; and it is tempting to infer that for low-risk groups (like children and young adults) natural infection alone or adding a single vaccine dose may more than suffice, as opposed to an aggressive vaccination strategy. However, inferences need to be cautious given the observational design of the study. Besides the documented previous infections, many other people probably had nondocumented infections that were either asymptomatic/oligosymptomatic or simply did not lead to testing; it is unknown whether prevalence, severity and resulting protection from these infections might have been different in vaccinated vs. unvaccinated people. The unvaccinated group with previous infection includes probably people with the most symptomatic, severe infections (that led to their documentation); it is unclear whether inferences can be extended to nondetected infections which are likely to be the large majority among children and young adults.

Seroprevalence studies may offer estimates of the extent of previous infections, even though, due to seroreversion, these may tend to be under-estimates. Illustratively, population seroprevalence studies (reviewed in ref. 33) have shown 68% seroprevalence in India in June–July 2021 (62% among the unvaccinated), 68% in Estonia in mid-June 2021 and 59% among the unvaccinated in Poland in May 2021. Some countries and locations have lower rates, for example seroprevalence in Quebec in January–March 2021 was only 15% (11% among the unvaccinated); and places that have evaded active epidemic waves to-date, for example New Zealand, probably cannot depend on any acquired natural immunity. Typically, young adults have higher exposure levels and infection rates than the average of the overall population.^{33,34} Therefore, one may cautiously estimate that about half of young adults in USA and in European countries with a high pandemic footprint and more than half of young adults in Central and South America, Western and Southern Asia and Africa have already been infected—with substantial heterogeneity across countries and across socioeconomic gradients within countries and within communities. Seroprevalence may be lower in children than in young adults^{33,34}; however, as schools have reopened in many countries, any differences may be already eroded. The need for vaccination

and optimal strategies may vary across settings with different rates of pre-existing infection and natural immunity.

10 | CONCLUDING COMMENTS

Table 2 summarizes the alluded arguments for and against vaccination in children and young adults. While many uncertainties remain about the optimal vaccination strategy across young age groups, improving vaccination rates of older and vulnerable individuals remains an uncontested

top priority everywhere. Moreover, vaccines may be redistributed, through initiatives such as COVID-19 Vaccines Global Access (COVAX), from wealthy countries that have largely vaccinated their vulnerable populations, as recommended also by the Director of the World Health Organization. Much more work needs to be done towards reverting global vaccine inequity.³⁵

Multiple factors and additional evidence may modify vaccination policies for children and young adults in the future. With mounting societal tension and fatigue from a long-standing pandemic, it would be unfortunate to make

TABLE 2 Arguments considered in the debate about vaccination of children and young adults

Types of considerations	Comments
Potential indirect effects	
Less disruption of education, return of families to normality, fewer outbreaks in the wider community, indirect protection of elderly and vulnerable people	Highly desirable, may be the key benefit from vaccinating youth; some evidence exists for modestly lesser infection and transmission risk with vaccination
Shift of the pandemic to higher age groups with vaccination of the young, infection of the older/vulnerable groups by unnoticed infected vaccinated youth	Potentially devastating; some evidence exists that vaccination may make more infections asymptomatic, thus unnoticed; over-confidence on vaccination may paradoxically increase infection rates through increased exposures (risk compensation)
Potential direct effects	
Lethal events from COVID-19 vs. from vaccination	Existing data suggest much higher risk from COVID-19 than from vaccination in youth; however, these data from the USA may over-estimate death risk from COVID-19
Nonlethal serious events from COVID-19 vs. from vaccination	Existing data suggest much higher risk from COVID-19 than from vaccination in youth; however, data from the USA on projected benefits may be over-estimates and data on adverse events from passive surveillance are probably under-estimates
Mild adverse events from vaccines	Very common, but short-lasting; may affect quality of life briefly
Long-term consequences of COVID-19	Important to document better
Long-term consequences of vaccination	While alarmism is not appropriate, it is very important to ensure careful studies with long-term follow-up to examine and exclude potential long-term toxicity
Modulating factors	
Sociodemographic risk stratification	Very strong across all ages, including youth; can modulate the risk-benefit ratio of vaccination substantially and may inform targeted protection
Risk stratification by comorbidities	Very strong across all ages, including youth; can modulate the risk-benefit ratio of vaccination substantially and may inform targeted protection
Future epidemic activity	Large uncertainty and difficult to predict
Emerging dominant variants	Large uncertainty both about whether/when such variants may emerge and whether currently existing vaccines will be effective against them or new vaccines will be needed
Strength and durability of natural vs. vaccine-induced immunity	Some preliminary evidence suggests that natural immunity is stronger and more durable than vaccine-induced immunity; requires corroboration and validation
Pre-existing immunity levels in the population from past infection	Varies substantially across countries and locations, but probably already very high in many countries and locations

decisions that are not evidence-based.³⁶ More frustration may be added, if there are reversals, for example if schools and universities cannot function again properly despite all good intentions and despite complex supportive measures that have been proposed besides vaccination (eg, phased re-openings, masks, ventilation, testing and more).³⁷ Optimizing vaccination recommendations would benefit from better evidence on the lethality of new emerging variants for children and young adults with and without comorbidities, the factors underlying sociodemographic inequalities, the long-term vaccine effectiveness for clinical outcomes and viral transmission, the long-term consequences of COVID-19 and the potential adverse events of vaccines in children and young adults.

CONFLICT OF INTEREST

None.

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