Possible risks and benefits of mRNA COVID-19 vaccines in preventing hospitalization of children aged 6 to 12 with and without comorbidities in the Netherlands

Abstract

Introduction

Children seem to be at very low risk for severe outcomes of disease following SARS-CoV-2 infection. Yet, children with certain medical risk conditions have a higher probability of hospitalization and severe disease compared to 'healthy' children. Currently, trials are ongoing to investigate if mRNA vaccines are safe and effective in children aged 6 to 12. This review will summarize evidence on direct health benefits and risks of mRNA COVID-19 vaccines in children aged 6 to 12 in the Netherlands, and evaluate the risk-benefit balance for both children with and without medical risk conditions.

Methods

Open source COVID-19 data were used in combination with literature. To quantify vaccine benefits, number needed to vaccinate (NNV) was calculated for the prevention of hospitalization. We used three different estimates for the proportion of children still at risk for severe COVID-19 based on recent seroprevalence data. We assumed children with prior SARS-CoV-2 infection were no longer at risk for severe outcomes due to (partial) immunity. Vaccine risks were calculated using recent data on mRNA vaccine associated myocarditis and anaphylactic shock.

Results

Direct benefits of vaccination are far greater for risk group children compared to healthy children. NNV for prevention of one hospitalization was 2553 (3394 to 2553) for healthy children and 365 (486 to 365) for risk group children, assuming 20% prior immunity in this age-group. If population prior immunity would be 50%, these numbers increase to 10,180 (13,523 to 10,180) for healthy children, and to 1464 (1963 to 1464) for children with medical risk conditions. Severe adverse events were comparable between both mRNA vaccines and between healthy and risk group children. Vaccinating all healthy children would most likely lead to 11 (4 to 45) cases of myocarditis and 5 (2 to 7) cases of anaphylactic shock, compared to 1 (0 to 4) and 0 (0 to 1) cases in risk group children, respectively.

Conclusion

In conclusion, according to available open source data and current literature, benefits of vaccination seem to outweigh the risks. Based on estimated NNV for influenza and varicella in the Netherlands, vaccinating only risk group children aged 6 to 12 with mRNA COVID-19 vaccines seems beneficial to prevent hospitalization in the Netherlands.

Laymen's summary

Introduction

It appears that some children develop serious events from COVID-19, much like adults. This is even more so for children with other medical conditions, such as heart diseases, diabetes or obesity. This is because they have an increased risk of severe disease, for which they may need to be admitted to a hospital. To stop the spread of the virus and prevent severe outcomes of COVID-19, vaccines have been developed and administered amongst people aged 12 and up. Currently, studies are seeing if vaccines might work well and safe in children, aged 6 to 12. This literature review looks into possible

risks and benefits of implementing these vaccines in children aged 6 to 12 in the Netherlands, to prevent hospitalization. For this study, a distinction was made between those children with increased risk of hospitalization and other children.

Methods
To study this, public data of confirmed infected children and hospital admissions was used, in combination with literature. However, the used data included only confirmed infected children in the Netherlands. It is believed that there are many unknown cases, simply because they could not be tested yet, at the start of the pandemic, or because they did not get tested, for instance because they did not know they were sick. Because we do not know the real percentage of children who got COVID-19, usefulness of vaccines to prevent hospitalization were calculated for three different situations. These situations included an assumption where it was believed that really 20% of children have been infected so far, one with 35% and one with 50% of previously infected children. This was done because this tells us something about how many hospitalizations we can expect, as eventually all children will get infected with COVID-19. To make an estimation, it is of course important to know if 50% of all children can get infected, and as many hospitalizations can be expected as we have seen so far, or if 80% can still be infected, and we expect 5 times as many hospitalizations.

Results
It is likely that vaccines are about as safe in children, as it is in adults. Most side-effects are not severe, but some can be, such as infection of the heart muscle or serious allergic reaction. However, these side-effects are very rare and often well-treatable. Therefore, benefits probably outweigh risks, as the risk of severe COVID-19 is much higher than the risk of these side-effects. If all risk group children would be vaccinated, most likely 1 heart muscle infection would occur and 0 serious allergic reactions. In healthy children, this would probably be 11 and 5 for these diseases. In both cases, these risks would be very small, based on the amount of vaccinated children.

To know how well vaccines would work in children, the amount of children who would need to be vaccinated to prevent one hospitalization was calculated for the three assumed percentages of infections. Vaccinating children who have underlying diseases seems far more effective than vaccinating healthy children to prevent hospitalization. In case 20% of the children have been infected, 365 would need to be vaccinated to prevent one hospitalization in this group, compared to 2553 healthy children. If 50% of the children so far would have been infected, this would increase to 1464 and 10,180, for each group.

Conclusion
In conclusion, COVID-19 vaccination for children aged 6 to 12 is most likely safe and probably works about as well as it does in adults. Vaccinating children with increased risk of hospitalization seems far more efficient and beneficial than also vaccinating all healthy children in the Netherlands.

Abbreviations

ARDS	– Acute respiratory distress syndrome
ARR	– Absolute risk reduction
CDC	– Centers for Disease Control and Prevention
CER	– Control event rate
CI	– Confidence interval
COPP Study	– Clinical features of COVID-19 in Paediatric Patients study
COVID-19	– Coronavirus disease 2019

EER	– Experimental event rate
mRNA	– Messenger RNA
MIS-A	– Multisystem Inflammatory Syndrome in adults
MIS-C	– Multisystem Inflammatory Syndrome in children
NNT	– Number needed to treat
NNV	– Number needed to vaccinate
PICU	– Paediatric intensive care unit
RIVM	– National Institute for Public Health and the Environment [Rijksinstituut voor volksgezondheid en milieu]
SARS-CoV-2	– Severe acute respiratory syndrome coronavirus 2
SmPC	– Summary of product characteristics

Introduction

In December 2019, the first person was diagnosed with Coronavirus disease 2019 (COVID-19), caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Since then, the virus has spread all over the world, affecting hundreds of millions of people worldwide. Common features of COVID-19 are cough, fever, shortness of breath, and fatigue, which are mild for a large proportion of infected people [2]. However, the spectrum of disease for COVID-19 can be broad with more severe disease, e.g. by destroying alveolar cells or affecting the liver, kidney, or gastrointestinal tract, occurring more often in more vulnerable groups such as elderly or people with comorbidities. This way, patients can suffer from acute respiratory distress syndrome (ARDS), but also non-pulmonary complications, such as septic shock and acute liver or kidney injury [3]. Another condition is long COVID, which patients can suffer from after having recovered from the acute phase of COVID-19. Duration of long COVID-19 varies from weeks to months, and clinical manifestations can vary between a severe form, e.g. with thromboembolic complications, and a nonspecific form, often presenting with fatigue and dyspnoea [4,5]. It is not surprising that the most common cause of death due to COVID-19 is respiratory failure [6].

Even though some studies suggest that children can suffer from long COVID [7,8], the spectrum of disease seems mostly different compared to adults. It appears clinical manifestations may be less severe in children, with 5.8% of cases being severe or critical, compared to 18.5% in adults, and a lower overall case fatality rate (0.05% vs 2.3%, respectively) [9,10]. However, increasing evidence seems to suggest that in rare cases, children can develop severe symptoms post COVID-infection, termed Multisystem Inflammatory Syndrome in children (MIS-C) [11]. Approximately one-third of children between 0 and 17 years who were admitted to a hospital in the Netherlands seem to be MIS-C cases, mostly affecting children aged 6 to 14 [12]. MIS-C is a severe clinical presentation of a variety of symptoms such as fever, gastrointestinal complaints, rash, and conjunctivitis, which often requires hospital or paediatric intensive care unit (PICU) admission. It also includes involvement of e.g. gastrointestinal, cardiovascular and respiratory organ systems. Due to this, it has similarities with Kawasaki Disease and Toxic Shock Syndrome and different definitions exist, further demonstrating the complexity of these clinical presentations [13–16]. However, what does seem clear is that children no longer seem to be making up around 2% of reported cases, which was the case in early 2020 [17], as there is an increasing trend in paediatric cases, logically accompanied by an increase in morbidity and mortality [18].

Based on literature, paediatric risk groups for COVID-19 include comorbidities comparable to those for influenza, even though evidence on asthmatic patients seems conflicting, with obesity as an additional risk factor [19]. These comorbidities seem to be associated with hospitalization or PICU admission, as

a worldwide systematic review showed a significant difference in presence of severe COVID between healthy and risk group children (0.21% vs 5.1%, resp.) [20]. On top of this, one study even showed that 5 out of 6 children with MIS-C had a pre-existing medical condition [21]. However, this finding does not seem conclusive. Other studies found 45% of MIS-C patients to have comorbidities [22], found no difference between healthy and risk group children [23], or even showed MIS-C patients to be mostly (previously) healthy children with mild or asymptomatic primary COVID-19 infection [24].

Thanks to the development of multiple COVID vaccines, many western countries are rapidly vaccinating their adult population as, for instance, estimated vaccination coverage has surpassed 85% in the Netherlands [25]. This is in large contrast to low and middle income countries, where vaccination coverage is much lower compared to the western world, which is accompanied by an increased need for vaccination [26]. However, as more western countries are vaccinating, and more studies are performed on vaccine efficacy after a third dose [27], less of these vaccines may become available for countries where people often have not had a first dose yet. Research is needed to ensure vaccines are not wasted, as this pandemic needs to be dealt with globally.

Taking this into account, together with the risks children may endure due to COVID-19, the question of utility and safety of COVID vaccination in children arises. As hospitalization numbers seem to climb slightly for children aged 6 and up [12], and vaccines are not approved for those younger than 12 years, researching the possibility of vaccinating children 6 to 12 seems like a logical step to take in combatting this pandemic. As Pfizer and Moderna's manufactured messenger RNA (mRNA) COVID vaccines are both advised for use in adolescents in the Netherlands [28,29], these are also most likely to be approved in younger children, and are thus of main interest for this review. As reported in the advisory letters of the Health Council of the Netherlands ('*Gezondheidsraad*') and the summary of product characteristics (SmPC) of both vaccines, side-effects of vaccines do occur [30,31]. These are often minor, e.g. local injection site pain, yet some severe side effects have been reported, including an excess risk of myocarditis, which especially younger males seem to be at higher risk of [32,33]. Based on an Israeli study, males aged 16 to 19 even had a standardised incidence ratio of 13.73 (95% CI 9.30 to 19.20) after second vaccine dose, compared to incidence during 2017 to 2019 [34]. Because of this, both safety and efficacy of vaccines in children should be devised using current literature. Therefore, this review will look at possible direct risks and benefits of mRNA COVID vaccines in children aged 6 to 12 in the Netherlands, by looking at children with and without increased risk of severe disease.

Methods

Quantities which were needed to answer the research question had to be determined based on literature or open source data. These quantities were: population size of the target group (i.e. all children aged 6 to 12 in the Netherlands, both those with and without previous SARS-CoV-2 infection), population size of the target group with medical risk conditions (i.e. those children in the population of interest who are part of one or more of the risk groups for COVID-19), the risk of hospital admission in the population of interest (separated for those children with and without a medical risk condition), the population at risk (i.e. the children in the population of interest without prior immunity due to infection), vaccine effectiveness of both mRNA vaccines, and risks of vaccine side-effects. Using this, the number needed to vaccinate (NNV) for prevention of hospitalization could be calculated to be compared to risks of vaccination.

To know the population size of the target group, i.e. the children aged 6 to 12 in the Netherlands, population dynamic data provided on the website of Statistics Netherlands (available at: https://opendata.cbs.nl/) was used [35]. In this review, 'healthy' children were defined as children

without any medical predisposition. Children belonging to the 'risk group' were defined as those with obesity or any comorbidity making them eligible for an influenza vaccine in the Netherlands. To estimate the size of these groups, both Dutch and English search terms for "*children*", "*obese*", "*medical condition",* and "*Netherlands*" were used. Using this search, a Dutch report was found which estimated the prevalence of obese children in the Netherlands [36]. Using a PubMed search for "*children*", "*influenza*", "*vaccination*", "*vaccine"*, "*immunization*", "*Netherlands*", "*pre-existing medical condition*", and "comorbidities", a paper was found, estimating the proportion of children eligible for influenza vaccination in the Netherlands [37]. These proportions were combined to estimate the population size of the target group with medical risk conditions.

The risk of hospital admission in the population of interest was estimated using open source COVID-19 data of the Dutch National Institute for Public Health and the Environment ('*Rijksinstituut voor Volksgezondheid en Milieu'* – RIVM) provided on their website (available at: https://data.rivm.nl/covid-19/ [accessed 8th October]) [38]. Using the RIVM COVID-19 national case file, data on all confirmed COVID-19 hospitalizations in the Netherlands could be used. This included hospitalizations up until October 7th 2021. Age groups specified in the dataset were 0 to 9 and 10 to 19. To further specify distribution of hospitalized COVID-19 cases by age, and thus know the proportion of hospitalized children aged 6 to 12, the daily updated website of the Clinical features of COVID-19 in Paediatric Patients (COPP) study (available at: https://covidkids.nl/scientific-dashboard/ [accessed 7th October 2021]) [12] was used. As none of these data included information on pre-existing medical conditions, search terms "*COVID-19*", "*preexisting medical condition*", "*comorbidities*", and "*children*" were used on PubMed. This provided a systematic review, looking at severe COVID cases, in which the difference in proportions of children with and without comorbidities was reported [20].

To be able to know which proportion of the 6 to 12 year old children were still at risk of getting infected with SARS-CoV-2, and possibly get severe disease and be hospitalized, it is of essence to know the proportion of children who had a prior infection, as these were assumed to be no longer at risk. A method to estimate this, is to look at seroprevalence in the population of interest. However, this is almost always a gross underestimation, partly due to the fact that a substantial proportion of children can be asymptomatic [13]. Additionally, many children have not been confirmed as actual cases in the first months of the pandemic, due to the fact that testing for COVID-19 was not possible. Therefore, the total number of confirmed infected children, estimated from the RIVM dataset, was not used to determine the at risk population. PubMed was searched for "*COVID-19*", "*seroprevalence*", "*immunity*", and "*children*". This provided a seroprevalence study from Switzerland [39]. However, as this estimate was most likely a considerable underestimation as well (unpublished CoKids-study Dr MLA de Hoog PhD), three estimated proportions for prior infected children were used: 20% was set as a lower bound, 35% as a middle estimate, and 50% as an upper bound. The prior immunized population, and thus the at-risk population, is also a measure for disease severity, as this is a proxy for the hospital admissions we can expect, based on how many hospital admissions have been observed. If all observed hospital admissions occurred in 20% of the child population, COVID-19 would be much more severe in children than when these hospitalizations occurred after infection of 50% of the population. This would increase the need for vaccination, as the expected hospital admissions yet to come would be much higher.

Vaccine effectiveness was based on SmPC of both vaccines, as were risks of reported side-effects [30,31]. Furthermore, risks of vaccine side-effects were searched on PubMed and using "*COVID-19*", "*side-effects*", "*adverse reaction*", "*vaccination*", and "*adolescents*". Papers reporting measures such as excess risk of severe adverse events after mRNA COVID-19 vaccines were included to assess possible

risks in the population of interest [32,40–42]. Based on the SmPC, severe adverse events included myocarditis and, anaphylactic shock, and facial paralysis, or Bell's palsy.

NNV, just as the number needed to treat (NNT), is a measure to quantify the reduction of an outcome of interest as a result of treatment or, in this case, vaccination. NNV is defined as the amount of people one would need to vaccinate in order to prevent a single case of the specified outcome of disease; in this case hospitalization. The NNV is calculated by taking the reciprocal of the absolute risk reduction (ARR). Here, the ARR is defined as the difference of two rates; the control event rate (CER), minus the experimental event rate (EER). The CER is the proportion of people with the specified outcome in the total population of interest, when no vaccine is implemented. The EER is the same proportion, but after implementation of the vaccine (Table 1). NNVs were calculated separately for 'healthy' children and children in a 'risk group' for all vaccines and set seroprevalences.

Table 1: Example of a table needed to calculate NNV for hospitalization in a single group, and for a single vaccine efficacy, shown with equations for CER, EER, ARR, and NNV

risk group children	Hospitalized	
	yes	no
Vaccinated	a	b
Not vaccinated	c	d
CER = c/(c+d)	ARR = CER – EER	
EER = a/(a+b)	NNV=1/ARR	

ARR, absolute risk reduction; CER, control event rate; EER, experimental event rate; NNV, number needed to vaccinate

The outcome used for calculating NNV was hospitalization due to COVID-19. NNV for prevention of a single hospitalized case was calculated for both Pfizer's and Moderna's mRNA vaccine. Pfizer/BioNTech reported vaccine efficacy based on data of adolescents aged 12 to 15 without evidence of prior infection [30]. Moderna has ongoing phase 2/3 trials, yet no reported preliminary efficacy estimates. Therefore, Moderna's overall vaccine efficacy from initial trials in an adult population were used [31]. NNV was calculated for a 'most likely', a 'best case' and a 'worse case' scenario, based on reported point estimates and upper and lower bounds of 95% CI of vaccine efficacy. NNVs were compared to estimated NNVs for hospitalization due to influenza [43,44] and varicella [45–48] in the Netherlands.

Results

According to data of Statistics Netherlands, 1,106,545 children aged 6 to 12 lived in the Netherlands on January 1st 2021 [35]. It is estimated that, in the Netherlands, children with e.g. pulmonary or hart conditions, diabetes, or other chronic conditions who are eligible for influenza vaccination, make up approximately 5.7% of the paediatric population [37]. As obesity (body mass index ≥ 30) is also a risk factor, and the prevalence of childhood obesity is approximately 3% in the Netherlands [36], this would come down to a total of 8.7% (n = 96,269) of children who would be in the risk group for COVID-19 in the Netherlands.

The RIVM dataset reported 386,469 (10.3%) positively tested children aged 0 to 19 [38]. A total of 594 hospitalizations were reported, 415 in the youngest and 179 in the oldest age group. Hospitalization proportions differed substantially between age groups, with 0.62% and 0.06% of confirmed COVID cases, respectively. As the age groups differed from the population of interest, i.e. children aged 6 to

12, and hospitalization rates clearly differed between groups, more information was needed on distribution of hospitalizations across age groups. Based on the COPP study [12], approximately 25% of hospitalizations occur in children aged 6 to 12. This would come down to 148 children aged 6 to 12 who have been hospitalized since the start of the pandemic. However, in what proportion of the totally infected population these hospitalizations occurred is naturally unknown, as only positively tested children were included in the dataset. A study which estimated seroprevalence at 19.5% for 9 to 13 year old children in March-April 2021, was used to estimate the lower bound of the prior infected population at 20% [39]. Two more proportions (35% and 50%) of prior infected children were chosen to account for uncertainty in knowing the at-risk population. In children aged 6 to 12, those who could benefit from vaccination included 885,236 (80% at risk), 719,254 (65% at risk), and 553 272 children (50% at risk) for the different scenarios.

Within these different proportions of prior immunized children, the total amount of confirmed SARS-CoV-2 cases, who were thus not eligible for vaccination, was the same. For children aged 6 to 12 this was assumed to be 114,238 (10.3%). The amount of 'missed' children (i.e. those who are assumed to have had a SARS-CoV-2 infection, but were not confirmed as such) for each proportion of prior immunization were thus 107,071 (9.7%), 273,053 (27.7%), and 439,035 (39.7%), resp. These are children assumed to be infected, yet still receive a vaccination, as previous infection has not been confirmed. It was assumed that these children are protected due to natural immunization, which could work as well as immunization after vaccination [49,50]. It was presumed that prior infection was the same for the healthy and the risk group, as the assumption was made that the probability of having had a SARS-CoV-2 infection since the start of the pandemic was the same for both groups. However, as this most likely is not the case for hospitalization, a distinction was made between healthy and risk group children. Unfortunately, no information about comorbidities was available in the data. Therefore, it was assumed that 40% of reported hospitalized children had comorbidities [23,51,52].

Risks of hospitalization due to COVID

As measures are being lifted in the Netherlands, eventually all children will be infected with SARS-CoV-2. It is important to have an idea of how many children would then be expected to be hospitalized to determine a, possibly detrimental, risk of COVID-19. Assuming a current seroprevalence of 20% in children aged 6 to 12, would mean that 885 236, of whom 77 016 (8.7%) part of a risk group, would still be at risk for COVID in the Netherlands. Assuming the observed 148 hospitalizations occurred in 20% of the children, this would mean that another 592 (0.07%) children would be hospitalized, of which 237 (0.31%) would be children in a risk group. If 35% of the child population would be infected, this would decrease to 275 (0.04%), 110 (0.18%) belonging to a risk group, out of a total 719 254 children. Assuming these data would actually reflect a 50% seroprevalence, another 148 (0.03%) children, of whom 59 (0.12%) children in a risk group, can be expected to be admitted to a hospital.

Risks of mRNA vaccination

According to the SmPC of Pfizer, side effects between adolescents (aged 12-15) and adults (16 and up) were similar, yet in some cases slightly more frequent in adolescents [30]. Severe adverse reactions which have been observed post-authorisation included myocarditis. Unfortunately, no evidence on this serious adverse event is available for children below the age of 12, as no vaccines have been approved. Therefore, other risk estimates were used, depending on which age groups were provided. For instance, myocarditis/pericarditis occurred in approximately 3 cases per one million doses, based on a meta-analysis [40], or even 10 to 50 cases per million persons in an Israeli health care organization compared to no vaccination [32]. However, this study also showed an excess risk of myocarditis following SARS-CoV-2 infection in a different study population. Still, age was not stratified in these studies, whilst other results have shown that the risk of myocarditis following mRNA vaccination

increases with younger age and is not increased for those belonging to COVID-19 risk groups [41,42]. Excess cases of myocarditis were assumed to be comparable between vaccines and were estimated to be 6.2 (95% CI 2.3 to 7.8) per one million administered doses in 12- to 39-year-olds [41]. As all children without confirmed as SARS-CoV-2 infection would be eligible for vaccine administration, and only 10.3% of the population is a confirmed case, a total of 992,307 (89.7%) children would be eligible for vaccine administration, who would be given almost 2 million doses in total. This would mean that approximately 1 risk group child and 11 healthy children aged 6 to 12 would develop myocarditis due to vaccine administration (Table 2). This is not taking a further association between myocarditis and age into account, which might lead to more myocarditis cases in practice, as this could play a role in children. Nevertheless, myocarditis has been reported as an adverse event in other widely implemented vaccines, such as those for hepatitis B, or inactivated influenza vaccines [53]. Even when taking possible post-vaccination myocarditis into account, COVID-19 mRNA vaccination still was recommended in a risk-balance analysis in all ages [42,54].

Anaphylactic shock was also observed as a serious, and life threatening adverse event. Therefore, even though this can be difficult to assess before vaccine administration, allergies to any of the vaccine components are a contraindication for these mRNA vaccines. This will not always be determined beforehand, meaning children might be at risk of anaphylactic shock due to COVID vaccination. According to updated estimates by the Centers for Disease Control and Prevention (CDC) [55], approximately 4.7 cases arise per million doses of Pfizer/BioNTech's mRNA vaccine and 2.5 for Moderna. This is comparable to another study, which assessed the excess cases of anaphylactic shock to be 4.8 (95% CI 3.2 to 6.9) and 5.1 (95% CI 3.3 to 7.6) for both mRNA vaccines, respectively [41]. These estimates are slightly higher than other vaccines, which are estimated to be around 1 to 2 cases per million doses [56]. However, as no information was known for adolescents, and the mean age was often around 40 years of age, translatability to children may be difficult. As demonstrated by another study, children may have approximately half to one-third of the risk for anaphylactic shock [57], possibly further decreasing the risk after mRNA vaccination in children. Assuming risk is reduced by half, vaccinating children aged 6 to 12 with mRNA vaccines would thus lead to about 2 to 8 cases of anaphylactic shock in fully vaccinated children in the Netherlands (Table 2). To effectively act on anaphylaxis, children should be observed for 15 minutes after vaccination, as is recommended in both SmPCs and current practice already for both mRNA vaccines. From a risk-benefit perspective, this approach is favoured over not vaccinating, and thus leaving people at risk for COVID-19, as anaphylaxis is almost always treated successfully [58]. Especially women and those with a history of allergic reactions seem affected by anaphylactic shock [59]. Due to the association with prior history of allergic reactions and female sex, those belonging to risk groups can be observed with more care, resulting in less life-threatening situations. Furthermore, it appears asthma patients may have an increased risk of anaphylactic shock [56] which could be approximately 1.5 to perhaps even a 5-fold risk compared to non-asthmatic patients [60,61]. However, as this group is so small compared to the risks, which are not excessively high, this will most likely have no great impact on expected adverse events. Therefore, risk of anaphylactic shock was assumed to be equal between risk group and healthy children.

Furthermore, facial paralysis, paresis or spasms were reported in three people in the Spikevax group, and once in the placebo group of Moderna's safety follow-up period, as well as four people vaccinated with Pfizer [30,31]. Based on these numbers, according to both vaccines' SmPCs, facial paralysis may affect up to 1 in 1000 vaccinees. Facial paralysis may thus occur in up to 906 and 86 children without and with comorbidities. However, two studies found no evidence of an association between mRNA vaccination and facial paralysis [41,62]. Furthermore, it is plausible that people can recover spontaneously, as clinical presentation seems similar to Bell's palsy [63].

Table 2: Risks and expected amount of serious adverse events after mRNA COVID-19 vaccination, provided for total population and split for risk group children and healthy children.

Serious adverse event following mRNA vaccination	Most likely risk per million fully vaccinated children (best case to worst case)	Most likely expected amount of affected children (best case to worst case)*
Myocarditis	12.4 (4.6 to 50)	12 (5 to 50)
Risk group children		1 (0 to 4)
Healthy children		11 (4 to 45)
Anaphylactic shock	4.7 (2.5 to 7.6)	5 (2 to 8)
Risk group children		0 (0 to 1)
Healthy children		4 (2 to 7)

**Added expected children with adverse events per group may differ from total due to rounding. Risk of adverse events are given per million fully vaccinated children, and given for a most likely, best case, and worst case scenario. Using these risks, the expected amount of children affected by these adverse events were calculated. This was again done for the three mentioned situations. COVID-19, Coronavirus disease 2019; mRNA, messenger RNA*

Direct benefits of vaccination

Efficacy estimates with 95% CI's, reported by Moderna and Pfizer in their SmPC, were used in this review: 94.1% (95% CI 89.3 to 96.8) and 100% (95% CI 75.3 to 100), resp. [30,31]. When looking at prevention of hospitalization due to vaccination for healthy children and risk group children, NNVs were calculated per vaccine for different prior infected population proportions. NNV for prevention of one hospitalization was 2553 (3394 to 2553) for healthy children and 365 (486 to 365) for risk group children, when using Pfizer in a setting with 20% of prior infected children. If the already infected population would be higher and turn out to be e.g. 50%, these numbers increased to 10,180 (13,523 to 10,180) for children not belonging to a risk group, compared to 1464 (1963 to 1464) for children in a risk group (Table 3). Estimated most likely vaccine efficacy of NNV for Moderna were all slightly higher compared to Pfizer, yet their spread between worst and best case scenario was smaller, yielding estimates with more precision. NNVs for risk group children were substantially lower compared to those for healthy children. All most likely NNV for risk group children were lower than the highest estimate for influenza hospitalization (NNV = 1695). Only Pfizer's worst case scenario for 50% prior infected children surpasses this estimation (NNV = 1963). All NNV estimates in healthy children are higher than that of influenza, with estimates for 50% prior infected population reaching towards or surpassing varicella's lowest estimate (NNV = 11,628) (Figure 1).

Table 3: NNVs for prevention of hospitalization in different settings for proportion of prior infected children and split per risk group.

Prior infected children	Risk group	Most likely NNV Pfizer (worst case to best case)	Most likely NNV Moderna (worst case to best case)
20%	No	2553 (3394 – 2553)	2713 (2858– 2634)
	Yes	365 (486 – 365)	388 (408 – 377)
35%	No	5491 (7307 – 5491)	5846 (6164 – 5663)
	Yes	785 (1041 – 785)	831 (881 – 815)
50%	No	10,180 (13,523– 10,180)	10,786 (11,469 – 10,535)
	Yes	1464 (1963 – 1464)	1542 (1629 – 1515)

NNVs are given for 'healthy' children and risk group children for a most likely, worst and best case scenario of vaccine efficacy [30,31]*. Risk group is defined as any child aged 6 to 12 with medical predisposition defined as a risk factor for COVID-19. 'Healthy' children are defined as those who do not have one of these risk factors. COVID-19, Coronavirus disease 2019; NNV, number needed to vaccinate*

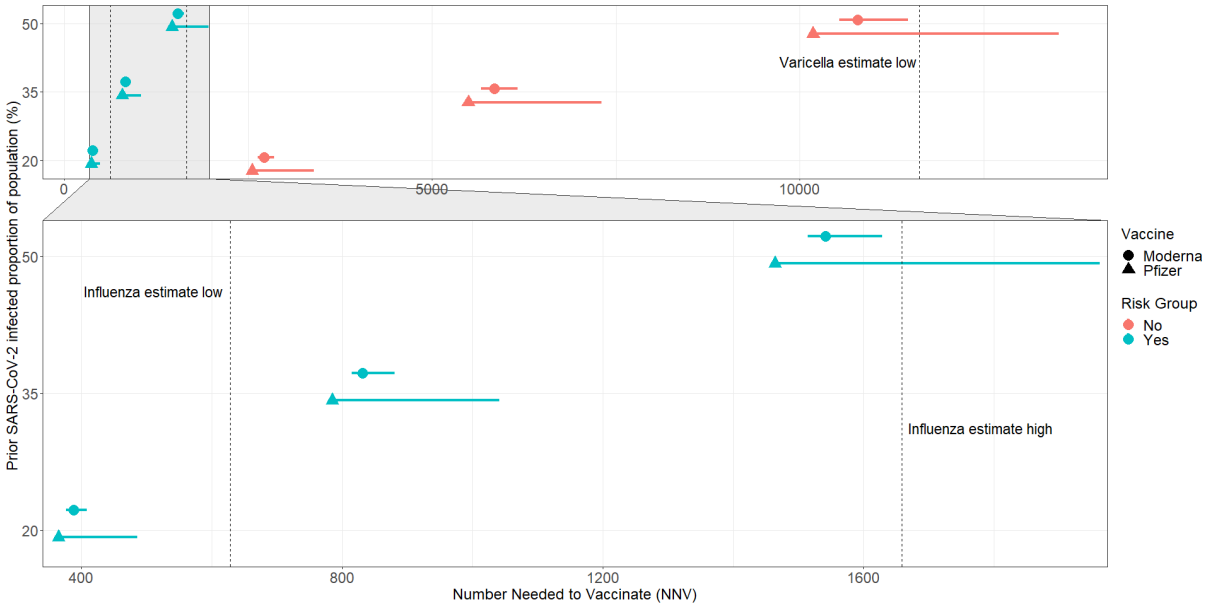

Figure 1: NNV for hospitalization due to COVID-19 in children aged 6 to 12 for Moderna and Pfizer mRNA vaccines, split per risk group and shown for three proportions of prior infected children. *Most likely scenarios for the NNV are shown with their best and worst case scenarios, based on reported vaccine efficacies of Pfizer and Moderna mRNA vaccines* [30,31]. *NNVs were calculated for healthy and risk group children in three different settings of prior SARS-CoV-2 infected children. Two estimated NNVs for prevention of hospitalization due to influenza* [43,44] *and the lowest estimate for varicella* [46] *are portrayed by dashed vertical lines. COVID-19, Coronavirus disease 2019; mRNA, messenger RNA; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2*

Discussion

In this review, vaccinating risk group children aged 6 to 12 with mRNA COVID-19 vaccines appears to lead to profoundly more direct health benefits than vaccinating healthy children in this age group, when looking at prevention of hospitalization in the Netherlands. Vaccinating all risk group children with Pfizer would prevent 237 (177 to 237) hospital admissions with 20% prior infected children, whilst risking 1 (0 to 4) myocarditis cases and 0 (0 to 1) children with anaphylactic shock. In a situation with 35% and 50% prior infected children, this vaccination strategy would prevent 110 (82 to 110) and 59 (44 to 59) hospital admissions, respectively, with the same risk of adverse events. For Moderna, at the cost of the same adverse events, prevented hospital admissions would be 223 (212 to 229), 104 (98 to 106), and 56 (53 to 57), for the different situations of prior infected proportions, respectively. When vaccinating healthy children with Pfizer, 355 (267 to 355), 165 (124 to 165), and 89 (67 to 89) hospital admissions can be prevented for the situations with 20, 35 and 50% prior infected children, respectively. For Moderna this will be 334 (317 to 344), 155 (147 to 160), and 84 (79 to 86), resp. Vaccinating healthy children with either one of these vaccines would risk 11 (4 to 45) children to develop myocarditis, and 4 (2 to 7) to suffer from anaphylactic shock. Severe adverse side effects are comparable for both vaccines and have negligible risks compared to their benefits.

For comparability of NNV, and being able to advise on possible implementation of mRNA COVID vaccines in the Netherlands, two vaccines were looked at: those for varicella and influenza. Varicella vaccination is not implemented in the Dutch vaccination program. Estimates for prevention of hospitalization vary substantially, with NNV ranging between 11,628 and 76,924 [45–48]. For varicella, implementation of a vaccination campaign would be comparable to that proposed for COVID-19

vaccination, as efficacy still seems to be approximately 90% after 14 years [64] and a single vaccination would thus suffice. All point estimates for NNVs for COVID hospitalization in risk group children are substantially lower than the lowest estimate for varicella.

On the other hand, in the Netherlands, influenza vaccination has been implemented in people with higher risk of serious disease. Estimates for prevention of hospitalization in these risk groups vary, as two different studies estimated the NNV at 628 [43] and 1695 [44]. However, interpretation of this annual vaccination is slightly different compared to the mRNA COVID vaccines, as these were assumed to only be administered once. Still, vaccinating solely the risk group children would seem beneficial, as NNVs mostly remain below the highest estimate of influenza NNV, or are at least comparable to this upper estimate. However, the estimated NNVs for healthy children seems to point to a different conclusion. It seems that implementing COVID-19 vaccinations in healthy children would be less effective than the highest estimate of influenza, with an increase of over 700 children needed to vaccinate for prevention of one hospital admission, assuming the prior infected proportion is 20%. This is still a large difference, yet might possibly be worth implementing due to nature of single vaccine administration. However, this proportion is the most conservative estimation used in this review, which will most likely have increased substantially before further research is published and national policies have been made accordingly. Therefore, the true at risk population will likely have decreased at the time, leading to rapidly increased NNVs for hospitalization, instantly diminishing the effectiveness of a possible vaccination campaign.

For these estimated NNV and advise on vaccine implementation, it is of great importance that vaccine efficacies do not diminish beyond the worst case scenarios. This could possibly change if, due to genetic drift, different strains of SARS-CoV-2 would arise and spread. For instance, when comparing the more virulent Delta (B.1.617.2) to the Alpha (B.1.1.7) variant, risk of hospitalization was doubled. Furthermore, studies regarding vaccine effectiveness against the Delta strain are not unanimous in their conclusion. Some studies show vaccines to remain protective, albeit possibly with a decreased effectiveness compared to the Alpha variant [65,66], although this evidence was not found to be statistically significant in all studies [67]. Nonetheless, vaccines seem to be most effective against severe infection, and thus have the possibility to still prevent hospitalization [65]. On top of this, not only vaccination protects against COVID-19, also prior infection seems to be associated with a comparable reduced risk of SARS-CoV-2 PCR test positivity [49]. Re-infection is even almost non-existent and the effect of natural immunity is comparable to vaccine efficacies [50]. Therefore, both vaccines and natural immunity play a role in combatting this pandemic as, even when new strains would arise, already infected or vaccinated children would most likely not need to be hospitalized. Therefore, it is not inconceivable to assume children would only require to be vaccinated once, in stead of annually, when prevention of hospitalization would be the primary objective.

As more research is being performed, COVID-19 also seems to be associated with MIS-C. To prevent this outcome of disease, the need for vaccination is stressed even more. However, as much is still unknown about MIS-C, so is information on the ability of vaccines to prevent this outcome. There is even a possibility that vaccines might induce MIS in adults (MIS-A). According to a series of case studies, 3 out of 6 adult patients presenting with MIS symptoms were vaccinated [68]. It is unclear if the immunopathology of MIS-A is similar to that of MIS-C and if vaccines might induce MIS-A or MIS-C [24]. Because of this, MIS-C was not used as possible outcome of disease. More research on MIS-C is needed and, as more vaccines continue to be administered amongst adolescents, more attention should be spend on the association between COVID-19 vaccination and MIS-C.

A limitation of this review is that only direct effects of vaccination were looked at. When indirect effects are also taken into account, it might be more beneficial to vaccinate children outside risk groups.

Indirect effects may eventually be small, as a large proportion of the Dutch adult population is already vaccinated [69]. Furthermore, evidence on waning immunity after Pfizer or Moderna vaccination is not undisputed and there is too little evidence to conclude this will play a role in the near future [70]. However, vaccinated people may have reduced periods of infectiousness after getting disease, limiting the possibility of spreading disease [66]. Furthermore, indirect effect of preventing another outbreak in winter could be an important factor for decision making, especially from the perspective of the Dutch government. This was also the case when the Health Council of the Netherlands advised to vaccinate adolescents of 12 to 17 [28]. Furthermore, this study solely focussed on prevention of hospital admissions. Further studies looking at e.g. long COVID or MIS-C could alter the conclusion of this paper.

Another limitation of this review, is the fact that COVID-19 vaccination may be given to immunocompromised patients, as they are part of the risk group, yet vaccine efficacy might not be as high in these patients [71]. Furthermore, the 8.7% of children who were estimated to be part of a risk group included asthmatic patients. In the Netherlands, this group makes up the bulk of the patients eligible for Influenza vaccination [37]. However, if further research would exclude asthmatic patients as a risk group, estimates of NNV based on the same data and assumptions would decrease for this group and increase for healthy children. This will thus most likely not alter the conclusion of this review.

Furthermore, as no information on comorbidities of interest was present, the assumption was made that seroprevalence was equal between healthy and risk group children. This was presumed because all children have the same chance of getting infected, as this is not determined by e.g. the presence of a medical predisposition. However, this might not truly be the case in a real life setting, as governments have acted on this pandemic with a number of measures for over 18 months. Children belonging to one of the risk groups might act on these measures with more regard than healthy children and, therefore, reduce their chance of getting infected with SARS-CoV-2. If this would be the case, relatively more risk group children would still be at-risk compared to healthy children. This would lower NNV for hospitalizations in risk group children, increasing the effectiveness of a possible vaccination campaign. Furthermore, in a situation without governmental measures, which we are slowly heading towards in the Netherlands, not implementing a vaccination campaign in these children would possibly mean these children have to keep acting on preventative measures, which would most likely severely affect their mental wellbeing due to e.g. limited social contact [72]. If this would be the case, a vaccination program in risk group children would be even more efficient based on a child's mental health.

In conclusion, according to available open source data and current literature, vaccinating children aged 6 to 12 with mRNA COVID-19 vaccines seems beneficial to prevent hospitalization in those belonging to a risk group in the Netherlands. This is true when at least 65% of the population is still at risk, and possibly for lower proportions, depending on vaccine efficacy. Vaccinating healthy children will most likely not be beneficial when looking at hospital admission. However, it is recommended to perform more direct and clinical evidence as support of this conclusion before real-life advise and policy should be made. This should include randomized clinical trials and cost-effectiveness analyses, making a distinction between children with and without a medical predisposition for increased risk of severe COVID. If preliminary results of Pfizer and Moderna's mRNA vaccines continue to show promising results in 12 to 15 year-olds, it could very well be beneficial to start trials in children aged 6 to 12. If approval is given for this age group, the Dutch government should act on implementing mRNA COVID-19 vaccines in children 6 to 12, most likely solely the ones at risk of serious outcomes. Selecting only this group is not solely beneficial due to much lower NNV, it would also prevent the excess use of vaccines, paving the way for higher vaccine availability in low and middle income countries.

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