Background document supporting the recommendations for selective vaccination of children 12-17 years old with COVID-19 vaccines in South Africa.

Problem statement

The current roll-out of COVID - 19 vaccines in SA targets everyone 18 years and over. Should children between the ages of 12 and 17 years be given COVID vaccines?

Considerations:

1. COVID-19 situation in children in SA:

As the COVID-19 pandemic has unfolded, evidence of children being infected by SARS-CoV-2 has emerged. Furthermore, information exists on the impact of the pandemic on children's education, mental health, and general well-being.

- By mid-June 2021, South Africa had conducted 12.3 million tests and detected 1.8 million cases. Children 19 years or younger accounted for 13.4% of tests conducted, 10.2% of new cases reported, 4.2% of COVID-19 associated hospital admissions and 0.7% of COVID-19 associated deaths. Since the onset of the third wave to the peak, the fraction of all COVID-19 cases aged 19 years or younger was averaging 14.6% as opposed to around 9% in the first and second waves. Half of the cases were occurring in older teens and adolescents 15 to 19 years, bringing the case rate in this group on par with adults older than 19 years.
    - https://theconversation.com/covid-19-in-children-the-south-african-experience-and-way-forward-164586
    - https://www.samrc.ac.za/sites/default/files/attachments/2021-01-29/COVID19specialNICDSurveillance.pdf

- HUTS seroprevalence study Nov 2020 - Jan 2021.
  0 to 9 years old 32/941 (3.4**%**) and 10-19 years old 156/941 (16.6**%**)
    - https://www.samrc.ac.za/sites/default/files/attachments/2021-03-31/NICD_Seroprevalence%20survey_Mar21.pdf

- Children and COVID: 1 March 2020 - 13 February 2021, N= 136 153 cases and 7987 admissions; median age 10.2 (1.4-17.2); 21% had at least one underlying condition; 9.2% and 3.8% of total cases and admissions respectively; approximately 6% ICU admissions and 3.6% CFR.
    - https://www.samrc.ac.za/sites/default/files/attachments/2021-02-24/DATCOV_Paediatric%20admissions_05Mar'20-13%20Feb%2721_23Feb21.pdf

2. *Published trials on COVID-19 vaccines in children:*

2.1. By mid-August there were four published trials that included participants aged less than 18 years. Two trials assessed the Pfizer/BioNTech mRNA COVID-19 vaccine and the other 2 refer to trials with inactivated vaccines.

2.2. The first study is a pivotal phase 2/3 trial of the safety and efficacy of the mRNA vaccine (BNT162b2) among 43,448 healthy participants aged 16 years of age or older in the United States, Argentina, Brazil, South Africa, Germany, and Turkey.

BNT162b2 was 95% effective in preventing COVID-19 (95% credible interval, 90.3 to 97.6). *Polack FP, et al. N Engl J Med. 2020 Dec 31;383(27):2603-2615.*

2.3. The second study was a phase 3 trial of the BNT162b2 vaccine among 2264 healthy adolescents aged 12 to 15 years old in the United States (Frenck 2021). Overall, the BNT162b2 vaccine in 12 to 15-year-old recipients had a favourable safety profile, produced a greater immune response than in young adults, and was highly effective against COVID-19. *Frenck RW Jr, et al N Engl J Med 2021 Jul 15;385(3):239-250.*

2.4. The third study is a phase 1/2 trial in one site in China of the safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in 552 healthy children and adolescents. The study found CoronaVac to be well tolerated and safe and induced humoral responses. *Han B, et al. Lancet Infect Dis 2021 Jun 28:S1473-3099(21)00319-4. doi: 10.1016/S1473-3099(21)00319-4.*

2.5. The fourth study is a phase 1/2 trial of the safety and immunogenicity of an inactivated SARS-CoV-2 vaccine (Bharat - BBV152) in healthy adults and adolescents (aged 12–65 years) at nine hospitals in India (Ella 2021). BBV152 was safe and immunogenic across all age strata. *Ella R, et al. Lancet Infect Dis 2021 Jul;21(7):950-961.*

In addition, Moderna reported that their initial analysis of their Phase 2/3 TeenCOVE study of mRNA-1273 in adolescents ages 12 to 17 years showed vaccine efficacy against COVID-19. *https://investors.modernatx.com/news-releases/news-release-details/moderna-reports-first-quarter-fiscal-year-2021-financial-results*

3. *Current global trends in vaccination of children:*

- A number of countries have issued directives for vaccination of 12-17 year old children.
    - https://www.reuters.com/business/healthcare-pharmaceuticals/countries-vaccinating-children-against-covid-19-2021-06-29/

- Countries including Canada, USA, Brazil and Chile do not have any restrictions in this age group.

- Some countries are limiting the vaccine to those as belonging to a high risk for severe COVID-19 group or living with older people at risk.

- WHO's Strategic Advisory Group of Experts (SAGE) has concluded that the Pfizer/BioNTech vaccine is suitable for use by people aged 12 years and above. Children aged between 12 and 15 years who are at high risk may be offered this vaccine alongside other priority groups for vaccination. Statement 14 July 2021.
    - https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice

- The South African Paediatric Association strongly recommends that children at risk of severe COVID-19 in the age range 12 to 17 years be vaccinated.

4. Ethical and regulatory framework

In South Africa, section 28(3) of the Constitution affirms that a child means a person under the age of 18 years. Section 28(2) stipulates that a child's best interests are of paramount importance in every matter concerning the child. In terms of section 28(1)(c), every child has the right to *inter alia* basic health care services. The Children's Act 38 of 2005 gives realisation to the rights of children as established in the Constitution. Its principles are based on the rights of children in international law. In line with these principles, all proceedings, actions, and

decisions to do with children must respect, promote and fulfil children's constitutional rights, the child's best interests and the rights and principles set out in the Children's Act, which include treating children fairly and equitably, and avoiding delays in taking actions or making decisions. Both the Constitution and the Children's Act places an obligation on the State to take action and put programs in place to make these rights a reality, e.g., in the case of the COVID-19 pandemic, the state must provide evidence-based prevention and early intervention programs to fulfil children's rights to protection against severe illness from the virus.

The COVID-19 pandemic has also disrupted schooling and education. This is even starker in disadvantaged individuals and communities where functional home schooling is difficult to achieve. Given the digital divide, many children in South Africa continue to be deprived of their rights to basic education as affirmed by section 29(1)(a) of the Constitution because they are unable to participate on the online education programs that privileged children have access to. Furthermore, the final two years of secondary schooling is critical in a child's life with successful completion being requisite for entry into a tertiary education institution. It is submitted that it is be in the child's best interests for the right to education to be realised, and that this right should not be limited.

The best interest's principle applies in all matters concerning the care, protection and well-being of the child. This means that the child's best interests must always be considered and prioritised. However, in certain situations other priorities may take precedence because while the child's best interests are paramount, they are not absolute and their operation will have to consider their relationship to other rights in the Constitution, which may necessitate a limitation of their ambit. The Children's Act describes factors that must be taken into account when making a decision that is in the best interests of the child. For the purpose of this Advisory, the relevant ones include:

- the child's age, maturity and stage of development;
- the child's physical and emotional security; and
- any disability or chronic illness that a child may have.

An additional factor to be considered is the child's ability to make an informed decision. The Children's Act recognises the child's right to respect for their evolving capacities in line with the United Nations Convention of the Rights of the Child (UNCRC). This means that as children grow and develop increasing competencies, they require less adult direction and support and have a greater capacity to take responsibility for decisions affecting their lives. The UNCRC recognises that children acquire these competencies at different ages depending on their environment, culture and individual life circumstances. Critical is achieving a balance between recognising their right to be listened to and their right to protection and support in accordance with their relative immaturity and youth. With regard to the consent provisions in the Children's Act, section 129 provides that the child may consent to his or her own medical treatment if he or she is over the age of 12 years and is of sufficient maturity and has the mental capacity to understand the benefits, risks, social and other implications of the treatment.

5. *Risk of severe adverse events following immunization – Cases of Myocarditis have been reported in association with mRNA vaccines in young person's, especially after the second dose.*

    - Myocarditis rates generally:

        - The 2015 Lancet publication cited the global estimate of incidence of myocarditis to be 220 cases per million person-years.

    - https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60692-4/fulltext
  - More recent estimates of US incidence, published in 2021, are lower at 10 to 100 cases per million person-years.
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8118666/pdf/main.pdf

- Myocarditis following mRNA vaccines:

  - As of August 11, 2021, VAERS has received 1,306 reports of myocarditis or pericarditis among people ages 30 and younger who received COVID-19 vaccine. Most cases have been reported after mRNA COVID-19 vaccination (Pfizer/BioNTech or Moderna), particularly in male adolescents and young adults. Through follow-up, including medical record reviews, CDC and FDA have confirmed 762 reports of myocarditis or pericarditis. CDC and its partners are investigating these reports to assess whether there is a relationship to COVID-19 vaccination.
    - https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

  - Crude reporting rates from CDC using vaccine administration data estimates the highest rate of myocarditis among male individuals aged 12 to 17 years (62.8 cases per million second dose).
    - https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm?s_cid=mm7027e2_w

TABLE 2. Individual-level estimated number of COVID-19 cases and COVID-19–associated hospitalizations, intensive care unit admissions, and deaths prevented after use of 2-dose mRNA COVID-19 vaccine for 120 days and number of myocarditis cases expected per million second mRNA vaccine doses administered, by sex and age group* — United States, 2021

	No. per million vaccine doses administered in each age group (yrs)†				
Sex/Benefits and harms from mRNA vaccination	**12–29**	**12–17**	**18–24**	**25–29**	**≥30**
Male					
Benefit					
COVID-19 cases prevented§	11,000	5,700	12,100	15,200	15,300
Hospitalizations prevented	560	215	530	936	4,598
ICU admissions prevented	138	71	127	215	1,242
Deaths prevented	6	2	3	13	700
Harms					
Myocarditis cases expected¶	39–47	56–69	45–56	15–18	3–4
Female					
Benefit					
COVID-19 cases prevented§	12,500	8,500	14,300	14,700	14,900
Hospitalizations prevented	922	183	1,127	1,459	3,484
ICU admissions prevented	73	38	93	87	707
Deaths prevented	6	1	13	4	347
Harm					
Myocarditis cases expected¶	4–5	8–10	4–5	2	1

Abbreviations: ICU = intensive care unit; VAERS = Vaccine Adverse Event Reporting System.
* This analysis evaluated direct benefits and harms, per million second doses of mRNA COVID-19 vaccine given in each age group, over 120 days. The numbers of events per million persons aged 12–29 years are the averages of numbers per million persons aged 12–17 years, 18–24 years, and 25–29 years.
† Receipt of 2 doses of mRNA COVID-19 vaccine, compared with no vaccination.
§ Case numbers have been rounded to the nearest hundred.
¶ Ranges calculated as ±10% of crude VAERS reporting rates. Estimates include cases of myocarditis, pericarditis, and myopericarditis.

  - A recent JAMA article reports 23 cases of myocarditis following mRNA vaccines in military recruits. The majority occurred after the second dose; median age 25 [20-51] years; 7 cases following Pfizer/BioNTech, and 16 following Moderna vaccines. The number was higher than expected among male military members after a second vaccine dose: 44 per million second doses to males.
    - https://jamanetwork.com/journals/jamacardiology/fullarticle/2781601

- Another publication from JAMA Cardiology reports a case series of 15 children with a median 15 years [range, 12-18 years] who were hospitalized with myocarditis after receipt of the Pfizer/BioNTech vaccine; 14/15 cases occurred after the second dose; 14/15 were boys.
    - https://jamanetwork.com/journals/jamacardiology/fullarticle/2783052

- In a nationwide mass vaccination setting (Israel), the Pfizer/BioNTech vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons)
    - Pfizer/BioNTech vaccine: myocarditis risk ratio, 3.24; 95% CI, 1.55 to 12.44;
    2.7 (1 to 4.6) events per 100,000 persons.
    - COVID-19 disease: myocarditis risk ratio, 18.28; 95% CI, 3.95 to 25.12;
    11.0 (5.6 -15.8) events per 100,000 persons.
    - https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110475?articleTools=true

- COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS): updated guidance regarding myocarditis and pericarditis reported with COVID-19 mRNA vaccines; 9th July 2021.
    - https://www.who.int/news/item/09-07-2021-gacvs-guidance-myocarditis-pericarditis-covid-19-mrna-vaccines

- Very rare cases of myocarditis and pericarditis have been observed following vaccination with the mRNA COVID-19 vaccines. These cases occurred more often in younger men and after the second dose of the vaccine, typically within few days after vaccination. Current evidence suggests a likely causal association between myocarditis and the mRNA vaccines.
- According to the data in the US Vaccine Adverse Events Reporting System (VAERS), approximately 40.6 cases of myocarditis per million second doses among males and 4.2 cases per million among females have been reported as of 11 June 2021 in persons 12 to 29 years of age who received the mRNA COVID-19 vaccines. For persons over 30 years of age, the reporting rates were 2.4 and 1.0 per million second doses, respectively, for males and females.
- Available data suggest that the immediate course of myocarditis and pericarditis following vaccination is generally mild and responds to conservative treatment.
- The benefits of mRNA COVID-19 vaccines outweigh the risks in reducing hospitalizations and deaths due to COVID-19 infections.

"Despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favourable balance for all age and sex groups; therefore, COVID-19 vaccination is currently recommended for everyone 12 years of age and older". Bozhurt B et al. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021;144:471–484.

Recommendations.

Three options were discussed at the VMAC

1. Universal vaccination for all children between 12 and 17 years of age with Pfizer/BioNTech vaccine.

OR

2. Vaccination of all children at risk for severe COVID-19 with Pfizer/BioNTech vaccine - see table below (modified from current UK Joint Committee on Vaccination and Immunisation recommendations).

OR

3. Selective vaccination approach (preferred option).

This third approach is based on the following considerations:

i. It is important to note that all / most research on COVID vaccines in children have been done in HICs. Given that little or no research has been done in LMICs – we should look at a possible selective approach and advise that more research be done in SA to monitor and evaluate implementation in this group. This is particularly so in the context of high rates of HIV, malnutrition, and other infectious diseases and co-morbidities. Research entities are encouraged to do this.
ii. The scarcity of vaccines and under-immunization of for example the high-risk groups such as those over sixty years of age.
iii. Balancing the risk of myocarditis after the second dose in younger persons if vaccinated against the risk of severe COVID-19 disease if not vaccinated.
iv. Protection of the older learner cohort of children in the secondary education sector and particularly the 16- to 17-year-old group who will be writing their matric examinations at the end of this year.
v. The potential benefit of a single dose in protecting against disease for at least probably around 4-6 months, if not longer. NACI (Canada) in their rollout extended the time period for the second dose up to 4 months after the first dose. The JCVI (UK) initially recommended a single dose for 16- to 17-year-olds to balance the risk and benefits of vaccination.
vi. In children with significant co-morbidities the benefits of vaccination appears to outweigh the risk of severe COVID if not vaccinated.

The selective approach for vaccination is thus recommended as follows:

- Children 12 to 17 years of age at high risk for COVID–19 receive 2 doses of Pfizer/BioNTech vaccine.
- 16- to 17-year-old children receive a single dose of Pfizer/BioNTech vaccine. The decision to give a second dose can be made at a later stage once more evidence of benefit and harm become available.
- Careful attention be paid to monitoring these children.

Table: Risk groups for vaccination in children 12-17 years of age (modified from current UK Joint Committee on Vaccination and Immunisation recommendations)

Disease	Comment
Chronic respiratory disease	Individuals with a severe lung condition, including those with asthma that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, bronchiectasis, cystic fibrosis, interstitial lung disease, and bronchopulmonary dysplasia (BPD).
Chronic heart disease and vascular disease	Congenital heart disease acquired heart disease (such as cardiomyopathy), or chronic heart failure in individuals requiring regular medication and/or follow-up for heart disease.
Chronic kidney disease	Chronic kidney disease at, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis.
Chronic neurological disease	Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease. including individuals with cerebral palsy, severe or profound and multiple learning disabilities , Trisomy 21 , epilepsy, motor neurone disease and related or similar conditions; hereditary

	and degenerative disease of the nervous system or muscles; or other severe neurological disability.
Diabetes mellitus and other endocrine disorders	Diabetes and Addison's disease.
Immunosuppression	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, HIV infection at all stages, genetic disorders affecting the immune system. Individuals who are receiving immunosuppressive or immunomodulating biological therapy. Individuals treated with or likely to be treated with systemic steroids for more than a month. Anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma and those with autoimmune diseases such as systemic lupus erythematosus or juvenile idiopathic arthritis who may require long term immunosuppressive treatments.
Asplenia or dysfunction of the spleen	This includes conditions that may lead to splenic dysfunction, such as homozygous sickle cell disease.
Morbid obesity	Body Mass Index (BMI) ≥40 kg/m².
Severe mental illness	Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment.
Adolescents in long-stay nursing and residential care settings	Adolescents in advanced care settings would be eligible for vaccination because they fall into one of the clinical risk groups above (for example learning disabilities). Given the likely high risk of exposure in these settings, where a high proportion of the population would be considered eligible, vaccination of the whole resident population is recommended.