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REVIEW ARTICLE

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Is there a role for childhood vaccination against COVID-19?

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Abstract

Tremendous efforts are undertaken to quickly develop COVID-19 vaccines that protect vulnerable individuals from severe disease and thereby limit the health and socioeconomic impacts of the pandemic. Potential candidates are tested in adult populations, and questions arise of whether COVID-19 vaccination should be implemented in children. Compared to adults, the incidence and disease severity of COVID-19 are low in children, and despite their infectiveness, their role in disease propagation is limited. Therefore, COVID-19 vaccines will need to have fully demonstrated safety and efficacy in preventing not only complications but transmission to justify childhood vaccination. This work summarizes currently tested vaccine platforms and debates practical and ethical considerations for their potential use in children. It also discusses the already deleterious effect of the pandemic on routine childhood vaccine coverage, calling for action to limit the risks for a rise in vaccine-preventable diseases.

KEYWORDS

childhood vaccination, COVID-19, COVID-19 vaccines, efficacy, safety, transmission of disease

1 | INTRODUCTION

More than 30 million cases of COVID-19 have already been reported worldwide in the last 9 months, and their continuous rise reflects the need to control disease spread. COVID-19 is caused by SARS-coronavirus 2 (CoV) and mainly characterized by respiratory symptoms and fever. Complications such as acute respiratory distress syndrome (ARDS) and death are primarily seen in the elderly and in individuals with co-morbidities, for example, obesity, arterial hypertension, or chronic kidney disease.[1-3] Children are more often pauci-symptomatic,[4-6] and a considerable proportion might even be co-infected with other respiratory viruses.[7] In rare cases, a post-infectious disease, characterized by multisystemic inflammation, Kawasaki-like symptoms, and acute heart failure, can occur,[8-10] but in general children have a very low risk of death.[4-6,11] Additionally, the incidence of COVID-19 disease is strikingly lower in children. Initial data from China showed that only around 1% of SARS-CoV-2 cases occurred in the pediatric population[12] and an Icelandic population screening could not evidence PCR-positive cases in children under the age of 10.[13] In the United States, PCR-positive cases in children aged 5-11 years were half as frequent as in adolescence,[14] a finding that was confirmed in a Swiss seroprevalence study.[15]

The role of children in disease transmission is still controversial. Infectious virus can be detected in nasopharyngeal swab of children of all age[16] and at similar or even higher concentrations than in adults.[17-19] There is evidence that children might have an insignificant role in disease transmission but rather get infected by adults or by household contacts.[20-24] However, schools were closed to help confine the pandemic, yet it still needs to be proven whether this specific measure (or the many others which were associated) was efficacious in slowing virus spread.[25-27]

Given the substantial impact of the COVID-19 outbreak on health systems and the socioeconomic burden following complete shutdowns of states in order to control the pandemic, a race for vaccines has started as soon as the first sequencing data of the virus became publicly available on January 12, 2020.[28] This was

even weeks before the pandemic had been declared on March 11, 2020.[29] Spike-protein S was identified as main vaccine target as it contains the receptor-binding domain that allows for host cell entry.[30] Neutralizing antibodies against the spike protein have been described following SARS-CoV[31] and most recently in SARS-CoV-2 vaccination.[32]

More than 200 vaccines are currently in preclinical tests using conventional methods (such as protein-based, subunit, or inactivated vaccines) and not yet commercialized vaccine delivery systems, such as nucleotide or viral vector vaccines.[33] The WHO has published guidelines regarding the prioritization for vaccines entering phase IIb/III clinical trials.[34] These guidelines also include criteria regarding safety and potential for efficacy in vulnerable individuals such as the elderly individuals with chronic diseases. The majority of the vaccine trials in phase II/III are focused on adult vaccination, and so far, only one vaccine is being tested in children.[35] However, the role of childhood vaccination in the containment of the pandemic still needs to be defined.

This opinion piece summarizes the current vaccine platforms that are being tested and their potential use in children and puts into perspective practical and ethical considerations for COVID-19 vaccination in children.

Key message

Incidence and disease severity of COVID-19 are low in children. In order to justify childhood vaccination, COVID-19 vaccines will need to have fully demonstrated safety and efficacy in preventing not only complications but also disease transmission. The already deleterious effect of the pandemic on routine childhood vaccine coverage calls for action to limit the risks for a rise in vaccine-preventable diseases.

2 | MAIN VACCINE PLATFORMS AND THEIR SAFETY PROFILE/CURRENT USE IN CHILDREN

Vaccine platforms may currently be characterized by their capacity at inducing strong $CD4^+$ and $CD8^+$ T-cell responses (to rapidly curtail viral infection and reduce complications) and/or high titers of neutralizing antibodies (possibly sufficient to also prevent infection, ie, reduce transmission). To date, genetic (mRNA/DNA) and vector vaccines mostly induce potent T-cell responses—with variable titers of neutralizing antibodies, whereas adjuvanted subunit vaccines may induce higher concentrations of neutralizing antibodies—but no $CD8^+$ T cells (Figure 1). The following described vaccine platforms are currently tested for the intra muscular route, and potential benefits of intranasal administration to elicit local mucosal immunity are discussed elsewhere.[36]

3 | RNA/DNA VACCINES

Nucleic acid vaccines use the host's cell transcription and translation machinery to express the vaccine antigen that is encoded by the injected nucleotide sequences. There are different mechanisms of delivery of the DNA or RNA (reviewed in Ref. 37). COVID-19 mRNA-based vaccines are delivered in lipids that play an important adjuvant role.

An advantage of this genetic vaccine platform is that vaccine design and production are very quick upon identification of the immunogenic protein and its sequence. However, a limiting factor for the broad use of this vaccine platform is the requirement for a frozen stockage (reviewed in Ref. 36). Also, there are no licensed RNA vaccines on the market so far, and very few safety data are available as only some phase I clinical trials have been published, for example, against rabies and influenza.[38,39]

For SARS-CoV-2, RNA-based vaccines are among the most advanced candidates. The mRNA-1273 vaccine, which encodes the prefusion stabilized form of the spike protein administered in lipid particles, triggered good antibody responses with pseudo-neutralization capacity in a dose-finding phase I trial in adults 18-55 years old.[40] However, dose-dependent reactogenicity was observed with local and systemic symptoms were frequent, especially after the second dose,[40] and restricted the vaccine dose for subsequent studies to 100 μg. Grade 3 (severe) events after administration of 100 μg were limited to local reactions and occurred in less than 10%.[40]

Enrollment of the phase II trial (n = 300 aged 8-55, n = 300 aged 55+) has been completed on July 8, 2020, and a large phase III study has started end of July 2020,[41] with 30 000 participants receiving two injections of 100 μg of mRNA-1273. In terms of risk groups, enrollment in a NIH-led phase I study in 30 older adults (56-70 years) and 30 elderly adults (aged 71+) has been completed and data will be published once available.[42] To date, there is no information available on any plans or preparation of pediatric trials.

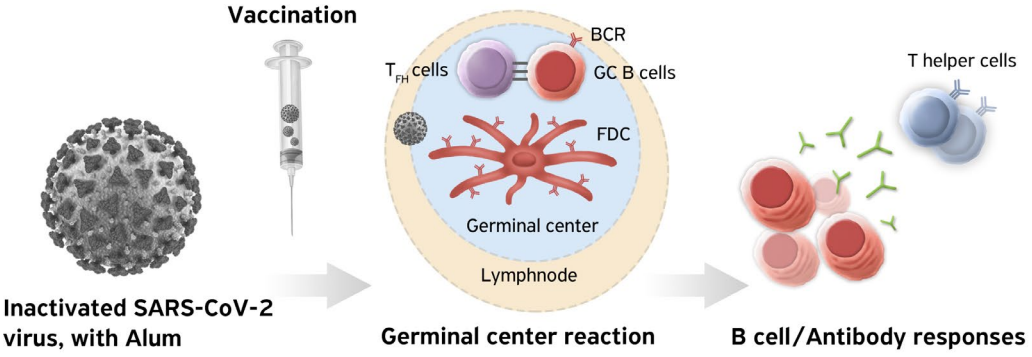
Four different lipid nanoparticle-formulated RNA vaccines (BNT162) have been tested, and phase I/II trial data are available on BNT162b1 that only includes the RBD. The vaccine elicited B- and T-cell responses up to day 43 ([43], preprint[44]), the safety profile showing dose-dependent transient but occasionally marked local and

FIGURE 1 Currently tested vaccine platforms and their mode of action. Schematic of inactivated, subunit vaccines and RNA and vector-based vaccines that are currently tested against COVID-19. Antigens are delivered as inactivated virus or subunit protein (first two rows) or as RNA that is either contained in a liposome or a viral vector (last two rows). Inactivated virus or subunit vaccines induce germinal center responses and thus B-cell/antibody and CD4 T-cell responses. RNA and viral vector vaccines can additionally induce CD8 T-cell responses—as the infected host cell will present the internally expressed protein on MHC-I molecules

Inactivated vaccine

PiCoVacc (CoronaVac)

SARS-CoV2-WIVO4



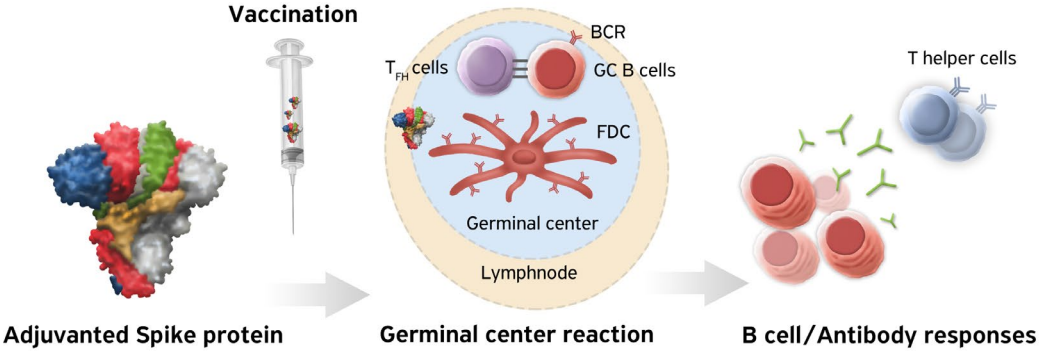
Subunit vaccine

NVX-CoV2373

with Matrix-M1 saponins

SCB-19

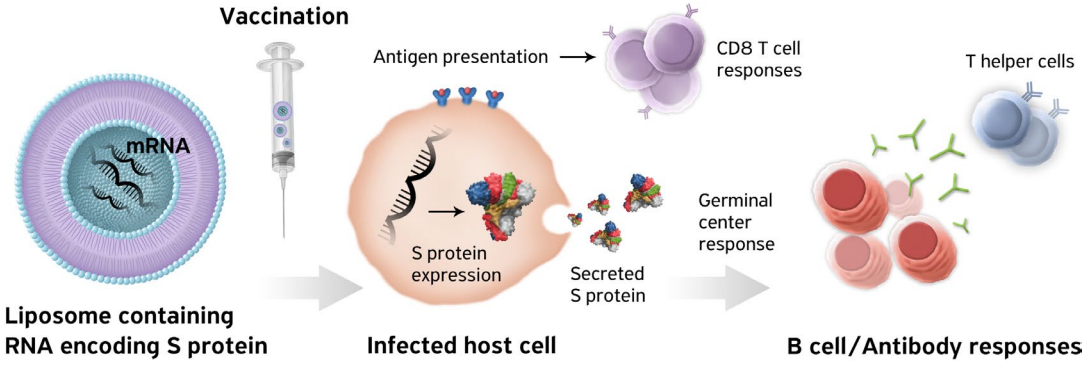
with AS03 or CPG1018 + Alum



RNA vaccine

mRNA-1273

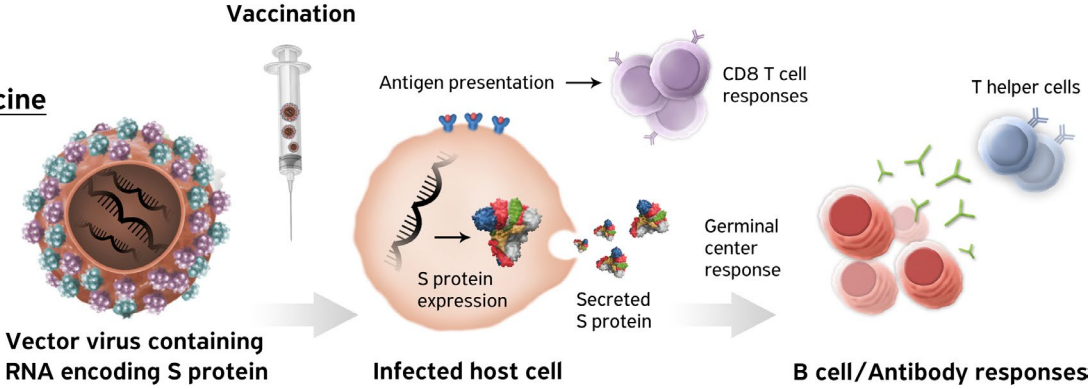
BNT162



Vector-based vaccine

Ad26.COV2.S.

ChAdOx1 nCoV-19



systemic reactions such as pain, fatigue, headache, and fever with Grade 3 events occurring in 2 of 36 participants.[43] Subsequently, the company decided to move forward with BNT162b2, covering the full-length spike protein, which is now being tested in a phase II/III trial.[45] DNA vaccines are currently in phase I/II testing.[46,47]

Given the paucity of clinical data for this vaccine platform, it is difficult to speculate how the reactogenicity and immunogenicity in children will compare to that of adults. The relatively modest induction of neutralizing antibodies suggests that they may better impact the risks of complications than of transmission, which could limit their use for childhood immunization given their low risk of complication.

4 | VIRAL VECTOR-BASED VACCINES

Viral vector vaccines insert into their genome the genetic sequence of the foreign viral antigen that is quickly expressed once the vector has infected the cell. This antigen is then either secreted, inducing B-cell/antibody responses, or digested within the targeted cells and presented to cytotoxic $CD8^+$ T cells, thus inducing potent $CD8^+$ T-cell responses.[48] A limitation of this approach is that the vaccinated individuals should not have pre-existing antibodies against the vector virus which would neutralize the vaccine before it can infect host cells. Therefore, xenotropic viruses such as chimpanzee's Adenovirus, modified vaccinia virus Ankara (MVA), fowlpox (FP), or vesicular stomatitis virus (VSV) are frequently employed.

In children, vector-based vaccines have been tested against malaria,[49,50] tuberculosis,[51] and Ebola.[52,53] The malaria vaccine candidate ME-TRAP, based on a heterologous prime-boost schema with MVA and FP9, was shown to be safe and relatively immunogenic,[54,55] but not efficacious.[50] Against tuberculosis, the MVA-Ag85A vaccine was safe in children (n = 24, 1-7 y/o) and adolescents (N = 12, 13-15 y/o), initiating $CD4^+$ T-cell responses that were moderately sustained at 6 months in adolescents.[51] Most advanced for pediatric use are vector-based vaccines against Ebola. The rVSVΔG-ZEBOV-GP vaccine was safe in children aged 6-12 years and adolescents[52] and may be used from 1 year onwards given the risks of EVD in young children. The quality and frequency of adverse events and in more than 10 000 children aged 1-5 years were similar as in adults.[56] Another vaccine based on a Chimpanzee adenovirus (ChAd3-EBO-Z) was tested in a phase II randomized placebo-controlled trial in 600 children. The vaccine was generally safe, although local symptoms such as pain were reported in around 42% and more frequently in the youngest (55% aged 1-5 years vs 31% aged 13-17 years). Systemic symptoms were described by half of the subjects, being mainly fever (1-5 years old) and headache (13-17 years old); however, severe events were recorded in only 1% of participants.[53,56]

It should be highlighted that the reactogenicity/safety profile of vector vaccines depends both upon the vector itself and the inserted foreign virus antigen—which may change its tropism. For example, vaccine-induced viral arthritis and skin vesicles were caused by VSV-ZEBOV[57] but not by other VSV constructs.

The most advanced viral vector platforms against SARS-CoV-2 are mostly adenovirus-based. The recombinant adenovirus type-5 vectored vaccine has been tested in 108 adults in a phase I trial[58] and in 382 adults in a phase II trial.[59] Adverse local reactions such as pain were reported in more than half of the participants, and systemic reactions in up to a third of individuals, most frequently being fever and fatigue, followed by cephalgia, myalgia, and joint pain. Grade 3 reactions were dose-dependent and observed in around 10%. Antibody and T-cell responses were still detectable at day 28 post-vaccination[58,59]; antibody titers were 4-fold lower in the presence of pre-existing anti-adenovirus antibodies at day 14, but increased to comparable levels at day 28.[59] Additional phase II trials are ongoing in adults[60] and planned in children.

Other recombinant adenovirus-based vaccines such as Ad26.COV2.S. were shown to be immunogenic in monkeys[61] and are currently in early-stage clinical testing.[62,63]

The simian adenovirus platform employed in the ChAdOx1 COVID19 vaccine has been previously established among others for MERS vaccination, showing persistent antibody titers in more than two-third of the 24 enrolled subjects after 1 year. However, neutralizing antibody titers were weak, only detectable at 1 month and in less than half of the individuals receiving the high dose.[64] In a simian adenovirus vectored influenza vaccine trial including healthy young (18-46) and elder adults (50+; n = 12 per group), T-cell responses after one dose returned to baseline at week 26 and a (heterologous) booster dose seemed to be necessary to confer long-term protection.[65]

ChAdOx1 COVID19 vaccine, also named AZD1222, is the most advanced. It was first successfully tested in monkeys.[66] In a phase I/II participant-blinded study, 543 healthy adults received ChAdOx1 nCoV-19[67] and antibody responses were assessed in a subset of patients. Anti-spike protein antibody titers remained modest (lower than in convalescent samples) but increased after a booster dose at day 28 (n = 10). No serious adverse events were reported,[67] and phase II/III trials are currently ongoing,[35,68] including a group of children aged 5-12 years. Again, their usefulness in children will depend upon their capacity to reduce transmission.

5 | PROTEIN-BASED, SUBUNIT, AND INACTIVATED VACCINES

Protein-based or inactivated vaccines are currently used in routine childhood immunization—mostly with aluminum salt adjuvants.

PiCoVacc, also called CoronaVac, is an alum-adjuvanted inactivated virus vaccine (SARS-CoV-2 strain CN2) that elicited broadly neutralizing antibodies in rodents and non-human primates and showed a dose-depended protection against challenge.[69] Clinical trials are currently ongoing in healthy adults and the elderly.[70-73] Another alum-adjuvanted, β-propiolactone inactivated SARS-CoV2-WIV04 strain was tested in a combined phase I and II trial.[74] A booster dose was given after 14 or 21 days in a total of 168 adults: Local reactions were observed in <15% of participants and systemic

reactions, mostly fever, in 6%, comparable to alum-only control groups, and no Grade 3 reactions were reported. More local reactions were seen in subjects with a 21-day interval between doses, yet immunogenicity in terms of antibody titers and neutralization was superior.[74] The theoretical risk of aluminum-based vaccines, which mainly induce $CD4^+$ Th2 responses, is that of eliciting antibody-dependent enhancement of disease.[75,76]

Designing and generating protein-based vaccine candidates take longer, as protein expression and proper folding and conformation need to be confirmed before testing. Hence, to date there are mainly preclinical data available for protein-based SARS-CoV-2 vaccination. An adjuvanted S-trimer vaccine (SCB-19) is currently tested with various adjuvants (ASO3 or CPG1018+ Alum or without adjuvant) in a phase I trial.[77]

The most advanced subunit vaccine (NVX-CoV2373) includes the full-length S-protein (fixed in a prefusion conformation) adjuvanted with Matrix-M1 saponins. It has been shown to be protective in animal studies (preprint[78,79]) and both safe and most immunogenic in a phase 1 trial with a prime-boost regimen.[32] Although comparing vaccine responses assessed with various assays is challenging, to date this vaccine candidate is the one eliciting the highest titers of fully neutralizing antibodies.[32] Phase I/II trials are currently ongoing,[80] and phase III trials will soon be initiated.

In summary, most of the current phase 3 trials are using new vaccine platforms or adjuvants for which very limited safety data are available in children. Apart from alum-based vaccines, commonly used in children, each candidate will thus require a most careful evaluation of its pediatric safety.

6 | ETHICAL CONSIDERATION OF CHILD VACCINATION

Besides practical and technical questions, it is imperative to discuss ethical considerations regarding childhood COVID-19 vaccination. Since the incidence and disease burden of COVID-19 are very low in children, vaccination should not be primarily performed for their self-protection but for that of the community, mainly the elderly or high-risk individuals. Hence, each vaccine will have to be thoroughly tested and proven safe before being administered to children to respect the risk-benefit balance. Furthermore, pediatric COVID-19 vaccines would need to be proven efficient in the interruption or reduction of virus transmission. To date, no NHP preclinical study has assessed the effect of vaccination in the prevention of transmission, and end-points of human COVID-19 vaccine trials focus on the induction of immunity and individual protection against disease. The current human trials unfortunately do not include measurement of viral loads as secondary end-point, nor of viral transmission as exploratory end-point. While we appreciate that children are not included in most of the phase 3 trials until there are sufficient safety data available in the adult population, we regret that the absence of information on viral transmission is a missed opportunity especially regarding the usefulness of vaccine candidates for the pediatric population. In the post-licensure phase, it will take long to evaluate to what extent vaccinated individuals remain transmitters of SARS-CoV-2.

Hence, vaccines with demonstrated safety and transmission efficacy data in children will not be available anytime soon, even if health authorities wished to recommend COVID-19 childhood vaccination, for example, to the few high-risk children.

While the world seems to be waiting for a COVID-19 vaccine "to return to normal life," confinement, restricted doctors' visits, and interruption of mass vaccine campaigns due to the COVID-19 pandemic have led to a concerning decrease in routine childhood vaccine administration. In the United States, childhood vaccine coverage rate has dramatically decreased to less than half in infants aged 5–18 months, compared to rates of around two-third in the same month of previous years.[81] Specifically, order rates for measles vaccine doses have decreased in the United States in the first trimester 2020 by more than 10%,[82] similar as seen in the UK during the period of social distancing.[83] Much more concerning are modeling data regarding the effect of suspended routine vaccination clinics in Africa, putting children and their families at a far higher risk to die of measles than of COVID-19.[84]

Hence, before we know whether a safe COVID vaccine effective against viral transmission becomes available and suited for use in the pediatric population, we call to focus on the best use of the safe and effective childhood vaccines we already have. Let's make sure we continue vaccinating healthy and vulnerable children according to recommended schedules to protect our young patients and avoid other epidemics in the future—with vaccine-preventable diseases like measles.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

Christiane Sigrid Eberhardt: Conceptualization (equal); Writing-original draft (lead); Writing-review & editing (supporting). **Claire-Anne Siegrist:** Conceptualization (equal); Writing-original draft (supporting); Writing-review & editing (lead).

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