Off-label prescription of BNT162b2 mRNA COVID-19 vaccine to <5-year-old children in the European Union

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1 INTRODUCTION

‘Off-label’ or ‘unlicensed’ use of medicinal products are those that are prescribed outside the terms of their authorisation by the regulatory agency in a given jurisdiction (i.e. unapproved indication, age group, posology, route or schedule of administration). As the highly transmissible Omicron variant of SARS-CoV-2 becomes prevalent in the US, the EU and elsewhere, Pfizer/BioNTech announced that the results of the ongoing phase 2/3 trial (NCT04816643) assessing its BNT162b2 mRNA vaccine in 0.5–4-year-old children will be delayed to test a 3-dose regimen. A debate has emerged in the USA on whether this vaccine could be ethically prescribed to this age group of children. Whilst some commentators considered its prescription to be ethically acceptable in vulnerable kids at high risk of developing severe COVID-19,1,2 recommendation against off-label paediatric use has been issued by the US Food and Drug Administration, American Academy of Paediatrics and Centers for Disease Control and Prevention. In addition, this latter has warned that off-label vaccine <5-year-old recipients may not be eligible for federal compensation in case of adverse events.1

2 RELEVANT FACTS ABOUT THE USE OF COVID-19 VACCINES IN THE EU

Regarding the situation in the EU, several facts should be considered. First, the advanced purchase agreements of the EU with manufacturers in 2020 stated that member states will be liable for the cost of redressing adverse reactions associated with COVID-19 vaccines.3 This situation is most likely replicated in the USA, the UK and elsewhere. Furthermore, since late 2021, the EU Parliament is considering creating an EU compensation fund for victims of COVID-19 vaccines.4 More than 435,000 and 4198 Europeans have reported adverse reactions or died, respectively, due to the BNT162b2 mRNA vaccine.4 To put these figures into perspective, it should be mentioned that as of early February 2022, data from the ECDC show that more than 570 million doses of this vaccine have been administered in the EU member states.5 Second, in the EU—as opposed to the USA, where both BNT162b2 and mRNA-1273 vaccines have been granted full approval—all COVID-19 vaccines are still under conditional marketing authorisation. Third, all vaccines have been (and, for some time, will be) administered following national public health authorities’ decisions. Only government officials—and those they allow—have access to these vaccines. Fourth, mRNA vaccines have already been administered off-label to millions of Europeans after receiving COVID-19 vector vaccines. These heterologous schedules as a second or booster (third) dose have been common in many EU countries long before the EMA and the ECDC recommend it in December 2021.6 Fifth, off-label vaccination of 5–11-year-old children with BNT162b2 mRNA vaccine happened in Austria before conditional marketing authorisation to the paediatric formulation was granted by the EMA.7 Since the dose for this age group was one third of the adult dose, healthcare providers had to reduce the...
dose to be given accordingly. Sixth, the vaccine claims compensation scheme mentioned above is applicable to claims related to adverse reactions following the off-label administration of the mRNA vaccines. Finally, when vaccination is not possible, other preventive measures such as well-fitted mask, social distance and regular hand-washing are not always possible or recommended depending on individual (e.g. age and condition/disease) and socioeconomic factors. So, for instance, wearing masks is only recommended for children ≥2-year-olds \(^8\) and overcrowded households have between 2 and 4 times the odds of confirmed SARS-CoV-2 infection compared with under-occupied households. \(^9\)

### 3 | BASIC FRAMEWORK FOR THE OFF-LABEL USE OF BNT162b2 mRNA VACCINE IN YOUNG CHILDREN

Considering the above, it is reasonable to believe that off-label prescription of BNT162b2 mRNA vaccine to <5-year-old children could be allowed in EU countries until the new formulation for this age group children is available in the EU, not to be expected, in the best scenario, before summer 2022. As has happened with unlicensed use of mRNA vaccines mentioned above, off-label prescription must be supported by national public health authorities, that should decide the requirements that any <5-year-old child must meet to be eligible. In all cases, expected benefit must outweigh the known and potential risks. The SARS-CoV-2 prevalent variant should always be taken into consideration.

When assessing potential risks, the focus should be on the relative risk in unvaccinated versus that of vaccinated <5-year-old children. \(^2\) In addition, expected adverse reactions (e.g. local reactogenicity, headache and fatigue) and rare adverse reactions in other age groups such as myocarditis and anaphylaxis must be considered. \(^10\) Interestingly, limited data suggest that two BNT162b2 mRNA vaccine doses have a 91% effectiveness against MIS-C in 12- to 18-year-old individuals. \(^11\) Data from the US surveillance systems showed a report rate of MIS-C among individuals aged 12-20 years that received one or two vaccine doses –85% of whom received the BNT162b2 vaccine—of one case per million, versus 200 cases per million SARS-CoV-2 infections in unvaccinated individuals in this age group. \(^12\) Although the risk of long COVID is uncertain in children, \(^13\) the possibility that COVID-19 vaccination will prevent it should also be taken into consideration.

The uncertainty regarding the appropriate dose could be solved by administering the 3 μg/dose that is being tested in the above-mentioned trial, but this should be decided on a case-by-case basis. As the BNT162b2 mRNA paediatric formulation (for 5-11-year-olds) contains 10 μg/dose, the appropriate dose to be administered to <5-year-olds needs to be individually calculated. Preparation of the vaccine dose requires specific training.

Only a limited number of highly vulnerable cases will be eligible to receive the vaccine. In this line, it will be important to define a risk-based approach for the administration of the vaccine to this vulnerable population—as has been done with the indication of monoclonal antibody treatment, focusing on children with obesity, medical complexity including genetic or neurodevelopmental syndromes, often associated with respiratory technology dependence and those severely immunocompromised. \(^14\) To ensure efficient delivery, more than one child should be vaccinated at the same time and this should ideally happen in a hospital setting. After obtaining child’s parents (or legal representative) informed consent, the report of the paediatrician supporting the vaccine prescription should be authorised by the hospital’s clinical ethics committee. In countries where the expected number of children eligible for vaccination will be very limited, the creation of an ad hoc expert committee might be a useful alternative. This approach will ensure that a third party—apart from those directly involved in each case—considers any eligible child as appropriate recipient of the vaccine.

### 4 | EPILOGUE

Parents should be aware of the importance of timely reporting of any adverse event and to attend the follow-up visits scheduled by their paediatrician. Furthermore, and importantly, all relevant data of these young, vaccinated children should be included in well-established national and international paediatric registries (e.g. European Society for Paediatric Infectious Diseases).

To prevent any misunderstandings among parents and paediatricians, public health authorities should inform the public on the general requirements to be fulfilled by eligible <5-year-old children to receive off-label COVID-19 vaccination. Paediatric professional associations should provide their members with specific information and guidance on how to initiate and complete the vaccination process. Proper management of parent expectations is critical to ensuring the smooth implementation of this off-label programme in any EU country.

### AUTHOR CONTRIBUTIONS

Dal-Ré conceived the idea and wrote the first draft of the manuscript. All authors provided comments and edits throughout the drafting process for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects included in it.

### CONFLICT OF INTEREST

Calvo and Neth are sub-investigators in a clinical trial of the Janssen COVID-19 vaccine in adolescents. Dal-Ré has no interest to declare.

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