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2024: Is There a Place for Freedom of Choice about Vaccination Based on Messenger RNA?

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Abstract

In 2024, COVID-19 vaccination became mandatory in Brazil for children aged 6 months to 4 years. The product available for this purpose is the BNT162b2 messenger RNA, whose potential risks are still not fully known compared to those of immunizations based on other platforms. This study assessed the current short term benefit/risk of BNT162b2 in pediatric population as a basis for discussion about the mandatory use or the freedom of choice on mRNA products in this age group. Methods. The epidemiology of severe acute respiratory syndrome was evaluated in Brazil based on freely available public data in the years 2022 and 2023, in children aged 6 months to 4 years. Results. The number needed to treat (NNT) with BNT162b2 to prevent one death from COVID-19 in this age group ranged from 208,856 to 548,246. The number needed to harm (NNH) of vaccine-associated death can range from 42,373 to 909,090. Conclusions. The results of this study indicate a borderline short-term benefit/risk balance of the BNT162b2 vaccine for the Brazilian population aged 6 months to 4 years. In this scenario, free informed choices regarding the use of mRNA products should be guaranteed for all.

Keywords

COVID-19, COVID-19 Vaccines, BNT162 Vaccine, SARS-CoV-2, Pediatrics

1. Introduction

Recently, in January 2024, the Brazilian Ministry of Health made it mandatory to vaccinate children aged between 6 months and 4 years against COVID-19, a disease caused by the SARS-CoV-2 virus that was responsible for the 2020-2023 pandemic [1]. Soon after, controversy arose in the country due to a survey made by the Federal Council of Medicine regarding Brazilian physicians' opinions about vaccination being mandatory.

The medical doubt was based on the fact that the only vaccine made available by the Brazilian government is the still-new BNT162b2 messenger RNA (mRNA) COVID-19 vaccine, whose long-term effects are unknown. Although there is widespread denial of the risk of genome alteration by mRNA products, it is known that mRNA retroposition can occur in human cells [2] and it has already been demonstrated *in vitro* with BNT162b2 [3].

The imposition of large-scale mandatory therapy with a new product should be based on a strongly favorable benefit/risk ratio, which has not been presented to date for the use of BNT162b2 in the population aged 6 months to 4 years. Therefore, this study aimed to analyze the incidence of SARS due to COVID-19 and other respiratory viruses in the Brazilian population aged 6 months to 4 years in the years 2022 and 2023 and to evaluate the short-term risk/benefit of BNT162b2 vaccination by the "number needed to treat" (NNT) and "number needed to cause harm" (NNH) in this pediatric population.

A clearly favorable risk/benefit balance in the short term can overcome the potential, but still uncertain, long term risks. But an unfavorable or borderline risk/benefit balance may lead one to think about the type of vaccine should be chosen at this moment. It is important to highlight that there are several other vaccines based on different platforms (vaccines with inactivated viruses, vaccines with proteins produced by molecular biology, and vaccines with a viral vector) that could be alternatives for mRNA vaccination in this age group.

Thus, the objectives of this study are: 1) To determine the incidence and mortality of SARS in the Brazilian population aged 6 months to 4 years in the years 2022 and 2023 and to determine the viral agents most frequently identified in those cases. 2) To relate SARS mortality caused by COVID-19 to BNT162b2 vaccination in the same pediatric population, estimating the protective effect of BNT162b2 by the odds ratio (OR). 3) To estimate the number needed to treat (NNT) with BNT162b2 to prevent one death from COVID-19 in this pediatric population. 4) To estimate the number needed to harm (NNH) associated with serious events of special interest and with death related to BNT162b2.

2. Material and Methods

This work used electronic spreadsheets with primary data from the registry of Brazilian SARS patients obtained from the Notifiable Diseases Information System (SINAN) by accessing InfoGripe, the Ministry of Health's public data portal [4]. Microsoft© Excel 365 was used to store and analyze the spreadsheets.

Only cases aged between 6 months and 5 years old were analyzed. For the purposes of identifying viral etiology, only cases in which viruses were identified using polymerase chain reaction (PCR) techniques or antigen research were included in the analysis.

Total Brazilian population in the age group between 6 months and 5 years old was 12,704,860, according to data from the 2022 Brazilian census [5].

The effectiveness of BNT162b2 in preventing SARS-CoV-2-related deaths was

estimated by the odds ratio (OR) calculated from the number of deaths in vaccinated children versus unvaccinated children.

Data on the occurrence of adverse effects associated with the BNT162b2 mRNA vaccine in children in this age group are scarce. The only clinical trial of BNT162b2 in children aged 6 months to 4 years followed less than 1000 children for six months after the third dose [6]. For this reason, the incidence of adverse events of special interest (clinically significant events with the potential to have a causal relationship with a vaccine) and mortality associated with BNT162b2 were calculated based on reviews of clinical trials in adult patients [7] and on data from the North American Vaccine Adverse Event Reporting System (VAERS) and V-safe [8], also in adult patients. In these studies, the frequency of adverse events was reported for each dose administered. To normalize the number of adverse events per number of people, it was assumed that each person received two doses of BNT162b2.

The number needed to treat (NNT) with BNT162b2 to prevent one death from COVID-19 and the NNT to avoid one SARS case due to COVID-19 were estimated from the odds ratio calculated in this study and the SARS incidence due to COVID-19 in the Brazilian population aged 6 months to 4 years [4]. The NNT with BNT162b2 to prevent one case of pediatric inflammatory multisystem syndrome (PIMS) was estimated based on data from Ouldali *et al.* [9] and Saied *et al.* [10].

The number needed to harm (NNH) was estimated based on general mortality rates calculated for 2023 and on the rates of adverse events and mortality related to BNT162b2, estimated for the adult population aged 16 years and over, based on Fraiman *et al.* [7] and Rosenblum *et al.* [8]. Sensitivity analyses were carried out for scenarios with an increase (2×) and a reduction (0.5×) in mortality from COVID-19, as well as for different values of mortality due to BNT162b2.

This research was based exclusively on the consultation of data freely accessible to the public (under Law No. 12527 of November 18, 2011), in aggregated databases, without individual identification. Due to these characteristics, it is exempt from analysis by the Ethics Committee for Research with Human Beings, in accordance with Resolution 510/2016 of the National Health Council of Brazil.

3. Results

3.1. SARS Incidence and Mortality in Brazil in Children Aged 6 Months to 4 Years

The incidence of SARS due to any cause and the absolute number of deaths due to SARS decreased between 2022 and 2023 in Brazilian children aged 6 months to 4 years (**Figure 1**).

Between 2022 and 2023, there was a significant reduction in the number of SARS cases in which SARS-CoV-2 (the COVID-19 agent) was identified (7678 cases to 2898 cases, a 62% reduction). The total number of SARS cases due to viral causes has remained stable because of the large increase in cases caused by

respiratory syncytial virus (RSV) (Figure 2).

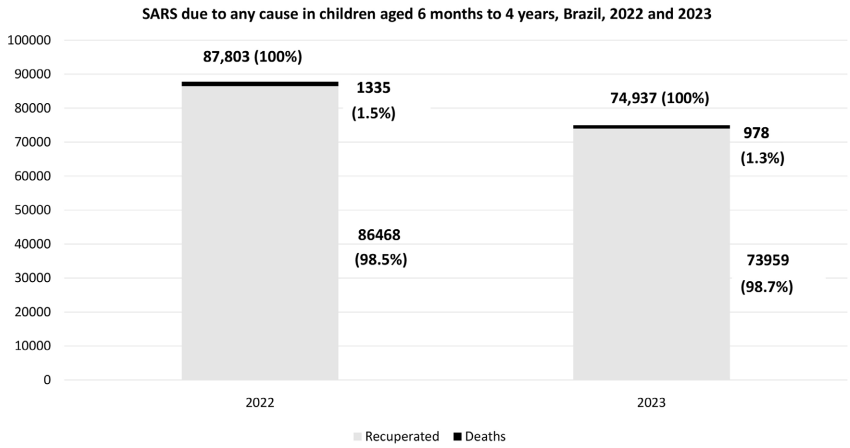

Figure 1. Number of SARS cases due to any cause and deaths in the years 2022 and 2023 in the Brazilian population aged between 6 months and 4 years. Source: InfoGripe-Opendatasus [4].

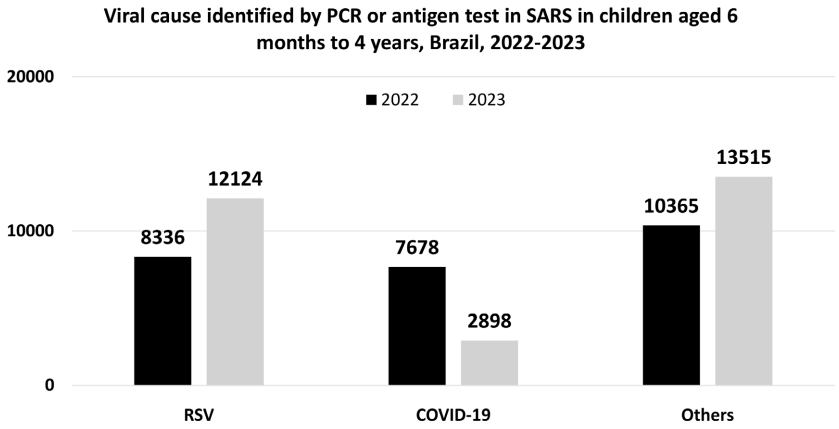

Figure 2. Number of SARS patients in which a specific viral agent was identified—COVID-19 (SARS-CoV-2), respiratory syncytial virus (RSV) and others—in the years 2022 and 2023 in the Brazilian population aged between 6 months and 4 years. Source: InfoGripe-Opendatasus [4].

The percentages of causative viral agents of SARS in children aged 6 months to 4 years in Brazil, 2022 and 2023, are shown in Figure 3 and Figure 4. There was a reduction of COVID-19 cases, both in absolute numbers and in relative importance among SARS cases.

A significant reduction in the number of deaths in children due to COVID-19 occurred from 2022 to 2023 (from 254 deaths to 82 deaths, a 67.7% reduction) (Figure 5).

3.2. Sensitivity Analyses of NNT with BNT162b2

Considering both years (2022 and 2023), there were 326 deaths of children aged between 6 months and 4 years from SARS due to COVID-19 (254 deaths in 2022

and 82 deaths in 2023). Of these 326 deaths, 14 occurred in children vaccinated against COVID-19, in relation to a total of 4943 vaccinated children (0.3% lethality). Among unvaccinated children, there were 312 deaths in relation to a total of 47,862 children (0.6% lethality). With these results, an odds ratio of 0.43 [0.25 - 0.74] was obtained for COVID-19 vaccination and mortality in children with COVID-19. Although the Brazilian children in 2022 and 2023 were vaccinated with both CORONAVAC and BNT162b2, BNT162b2 was used in approximately 75% of the cases in which the vaccine manufacturer was recorded. Due to this predominance of BNT162b2, for simplification purposes, in this study, the calculated odds ratio was assumed to be the value for BNT162b2.

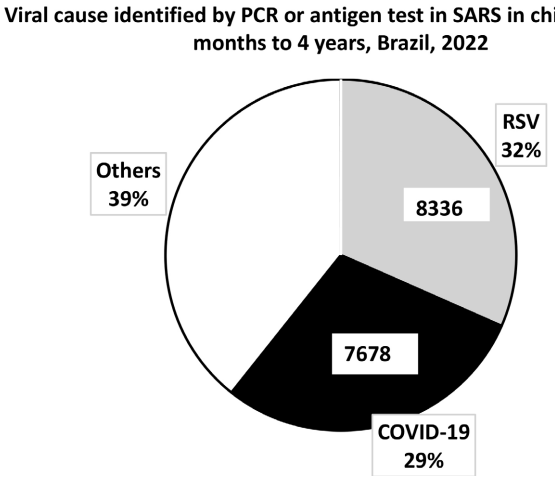

Figure 3. Percent distribution of specific viral agents identified in SARS patients in children aged 6 months to 4 years in Brazil in 2022. COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV) and others. Source: InfoGripe-Opendatasus [4].

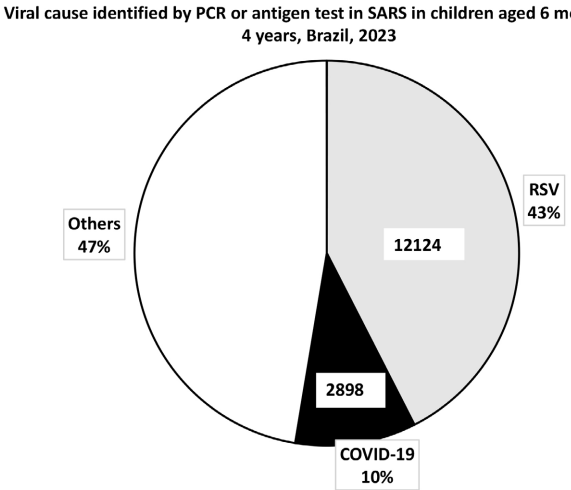

Figure 4. Percent distribution of specific viral agents identified in SARS patients aged 6 months to 4 years in Brazil in 2023. COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV) and others. Source: InfoGripe-Opendatasus [4].

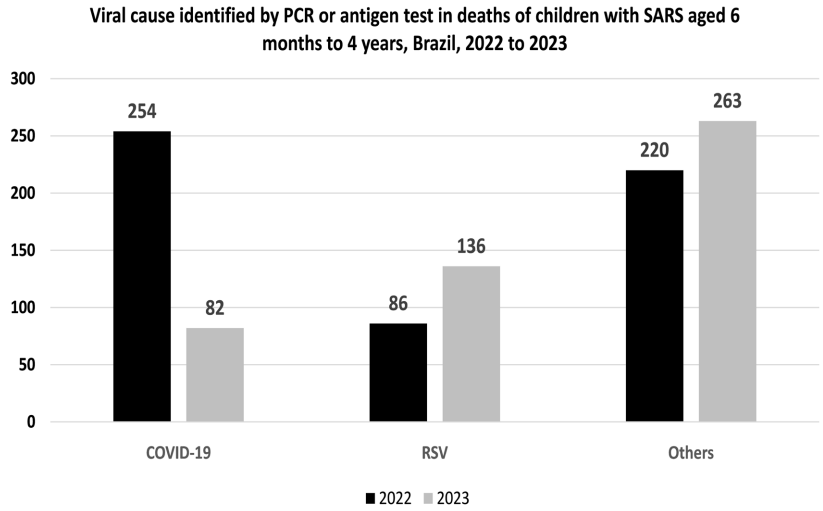

Figure 5. Number of deaths associated with SARS with the identification of a specific viral agent—COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV) and others—in the years 2022 and 2023 in the Brazilian population aged between 6 months and 4 years. Source: InfoGripe-Opendatasus [4].

According to the 2022 Brazilian census, 12,704,860 children constitute the Brazilian population under 5 years of age [5]. For simplification purposes, the same number will be considered for the two years, 2022 and 2023, for the population aged between 6 months and 4 years.

In 2023, the SARS mortality rate due to confirmed COVID-19 in Brazilian children aged between 6 months and 4 years was 6.5/1,000,000 children.

Considering that the OR of BNT162b2 to prevent death is 0.43 and mortality of COVID-19 in children is 6.5/1,000,000, we obtained an NNT of 269,906, corresponding to the number of children who needed to be inoculated with BNT162b2 to prevent one death from COVID-19 in this group.

However, it is possible that mortality due to viral causes is underrepresented, given that a specific viral agent was identified by PCR or antigen research in only one-third of SARS patients (in 2023, a viral agent was identified in 28,537 of 74,937 SARS cases).

Among SARS patients whose virus was identified in 2023, 10.2% had COVID-19. Assuming that the same proportion remains in all 74,937 SARS cases, there would be an estimated maximum of 7644 cases of SARS due to COVID-19 in 2023.

Additionally, in 2023, 82 children died in a total of 2898 patients confirmed COVID-19 cases (2.8%). Applying this same case fatality rate to the estimated maximum total of 7644 COVID-19 cases, there would be an estimated maximum of 214 deaths from COVID-19. This value would lead to a maximum estimated death rate of 16.8/1,000,000.

Considering the same OR = 0.43 and the maximum mortality estimated at 16.8/1,000,000, one obtains an NNT of 104,428.

It is likely that the NNT at the end of 2023 will fall between one of these two extremes. Mortality from COVID-19 should be higher than that calculated from cases in which there was viral identification, but the underreporting rate should be proportionally lower for COVID-19 than for other viruses, given that the availability of PCR and antigen research exams for SARS-CoV-2 was probably higher than for other viruses in this period.

Sensitivity analyses allow us to estimate different scenarios for 2024. In a scenario of a progressive decline in the incidence of COVID-19 in children, if mortality from COVID-19 is halved in 2024, the NNT to prevent one death will fall between the extremes of 548,246 and 208,856 (half of the extreme values estimated for 2023).

In this study, there is no available data on vaccination coverage in all children aged between 6 months and 4 years in Brazil, as only those who developed SARS were included in the database analyzed. To estimate this vaccination coverage, one used the vaccination coverage rate among children with SARS caused by viral agents other than SARS-CoV-2, assuming that this rate should be analogous to that of the general population of children in the same age group. This rate was 14.4%.

Considering 14.4% of vaccination coverage and considering the records of 2898 SARS cases due to confirmed COVID-19 in the age group of 6 months to 4 years in 2023, it was possible to estimate that the odds ratio for preventing SARS due to COVID-19 associated with BNT162b2 vaccination was 0.89 [0.80 - 0.99].

The incidence of SARS with COVID-19 in 2023 was 228/1,000,000, and the calculated NNT to prevent one case of SARS was 39,863.

The worst-case scenario was again adjusted to a maximum total 7644 SARS cases due to COVID-19 (10.2% of the 74,937 total SARS cases). The incidence of SARS due to COVID-19 was calculated as 601.6/1,000,000. In this scenario, the NNT of BNT612b2 to prevent one case of SARS would reach 15,119.

To calculate the NNT of BNT162b2 associated with the prevention of PIMS, data from Oudali *et al.* [9] and Saied *et al.* [10] were used. The current incidence of all cases of COVID-19 in Brazil is 60.6 cases per 100,000 inhabitants [11]. Assuming the same incidence value in children and correcting for an expected notification rate of 10% of total cases (corresponding to the last estimate made in Brazil in 2020) [12], one can estimate the incidence of 606 COVID-19 cases per 100,000 children. According to Oudali *et al.* [9], considering that the incidence of PIMS in unvaccinated people after COVID-19 infection was 133/1,000,000, it was possible to estimate an incidence of 0.8/1,000,000 PIMS cases in Brazil. With the odds ratio of 0.04 [10], it was possible to calculate the NNT with BNT162b2 to avoid one case of PIMS: 11,363,644. If the COVID-19 case notification rate is only 1% of the total cases, the PIMS incidence is 8/1,000,000, and the NNT is 1,136,372.

3.3. Sensitivity Analyses of NNH with BNT162b2

Table 1 presents mortality data related to the use of BNT162b2 extracted from Rosemblum *et al.* [8] compared to general mortality data for the North American

population in 2021 extracted from the USA Centers for Disease Control (CDC) [13]. Three age groups (16 - 17 years, 18 - 49 years and 50 years or older) were analyzed to determine age-adjusted mortality in both groups (adverse events related to BNT162b2 and the general population). Of note, there were not differences between age-mortality rate and the unadjusted mortality rate in the vaccinated group and the general population.

However, proportion of deaths in the youngest (16 - 17 years) was significantly higher in the BNT162b2 group than in the general population in the same age group: 0.3% vs 0.1%, p = 0.02, Chi-Square.

Table 1. BNT162b2-associated and general mortality in North American population, 2021.

Data source	Table Column Head				
	Age group (years)	Population, n (%)	Deaths, n (%)	Mortality /1,000,000	Age-adjusted mortality /1,000,000
BNT162b2 [8]	16 - 17	2,682,928 (3.2)	6 (0.3)	2.2	
	18 - 49	37,499,663 (44.9)	151 (7.7)	3.9	
	50+	43,400,982 (51.9)	1813 (92.0)	41.8	
	Total	83,583,573 (100.0)	1970 (100.0)	23.6	23.6
General Pop. [12]	16 - 17	33,662,129 (3.3)	15,452 (0.1)	459.0	
	18 - 49	519,202,197 (50.7)	1,030,037 (8.3)	1891.0	
	50+	470,588,856 (46.0)	11,330,405 (91.6)	24,077.1	
	Total	1,023,453,182 (100.0)	12,375,894 (100.0)	12,092.3	12,096.6

Source: Calculated based on data from Rosemblum *et al.* [8] and the USA Center for Disease Control (CDC) [12]. Pop., population. BNT162b2 refers to events recorded as adverse reactions to the use of the product.

Table 2 shows the main causes of death related to the use of BNT162b2, extracted from Rosemblum *et al.* [8], compared to the main causes of nonaccidental death in the general North American population in 2021, extracted from the USA Centers of Disease Control (CDC) [13].

Age-adjusted all-cause mortality related to BNT162b2 adverse events could be calculated from data presented by Rosemblum *et al.* [8]: 23.6/1,000,000 vaccinated people. It is clear that this mortality rate decreases with lower age: it is 41.8/1,000,000 in the population aged 50 or over, 3.9/1,000,000 in the population aged between 16 and 49 years, and 2.2/1,000,000 in the youngest age group analyzed (16 - 17 years).

In Brazil, it was possible to obtain data on the number of deaths and population in the 1 - 4 age group. In 2021, there were 5021 deaths for the total population of 11,780,737 children in this age group [5] resulting in a mortality rate of

426.2/1,000,000. For simplification purposes, this value was used to represent the mortality of the Brazilian population in the age group from 6 months to 4 years. It was decided not to use the total population under 5 years of age to avoid the increased bias caused by the inclusion of perinatal mortality.

Table 2. Most common causes of nonaccidental death in deaths associated with BNT162b2 and in general mortality in the North American population, 2021.

Cause of death	Group		p
	BNT162b2: Deaths, n (%) [8]	General Population: Deaths, n (%) [12]	
Heart disease	456 (21.8)	2,706,931 (21.6)	0.758
COVID-19	240 (11.5)	767,724 (6.1)	**<0.01**
Cerebrovascular disease	129 (6.2)	620,969 (4.9)	**<0.01**
Cancer	57 (2.7)	2,406,438 (19.2)	**<0.01**
Chronic respiratory disease	27 (1.3)	611,464 (4.8)	**<0.01**
Total	2086	12,542,003	

Source. Calculated based on data from Rosemblum *et al.* [8] and the USA Center for Disease Control (CDC) [13]. BNT162b2 refers to events recorded as adverse reactions to the use of the product.

Assuming an additional mortality rate in the pediatric population aged 6 months to 4 years with the same mortality value associated with BNT162b2 in the adult population (23.6/1,000,000) over the base mortality of 426.2/1,000,000, the NNH obtained is 42,373. This value indicates that one death associated with the use of BNT162b2 occurred for every 42,373 children inoculated with this product. But this is an unrealistic scenario.

A more likely scenario is that the mortality rate associated to BNT162b2 in children is lower than that in adults. The youngest age group in which a mortality rate associated with BNT162b2 could be determined was the 16 - 17 age group (2.2/1,000,000). Admitting this same value for the age group from 6 months to 4 years, the NNH obtained was 454,545.

The BNT162b2 mortality rate in young children is probably even lower than that in adolescents. Assuming a scenario in which the BNT162b2 mortality rate in children aged 6 months to 4 years is half the rate observed in adolescents aged 16 - 17 years (1.1/1,000,000), the NNH obtained is 909,090.

The occurrence rate of serious adverse events of special interest associated with BNT162b2 can be calculated at 10.1/10,000 vaccinated people (1,010/1,000,000), based on data presented by Fraiman *et al.* [7]: 27.7/10,000 vaccinated people versus 17.6/10,000 in the placebo group. Considering these values, the NNH can be calculated as NNH = 990 (number of people needed to be vaccinated to cause a serious adverse event of special interest). The most frequent serious adverse events of special interest associated with BNT162b2 was coagulation disorder (320/1,000,000 above the placebo group rate), acute cardiac injury (210/1,000,000 above the placebo group

rate), and acute kidney injury (110/1,000,000 above the placebo group rate) [7]. The rates of adverse events in the pediatric population are not known either, and they are likely to be lower than those in the adult population. For sensitivity analysis, if the rate of serious adverse events in children above the placebo group rate was assumed to be 1/10 of the rate observed in adults (101/1,000,000), with the same reduction in the placebo group rate, the NNH obtained was 9901.

A comparison between the different scenarios of NNT and NNH of BNT162b2 for preventing death from COVID-19 or for causing death due to an adverse effect of the product and of NNT and NNH of BNT166b2 for preventing SARS or for the occurrence of serious adverse events related to BNT166b2 in children aged 6 months to 4 years, obtained by means of sensitivity analysis, is presented in Table 3.

Table 3. Comparison between extreme NNT and NNH scenarios of BNT166b2 for the pediatric population aged 6 months to 4 years.

Comparison	Sensitivity analysis	NNT	NNH	NNT:NNH
Prevention of death from COVID-19 versus occurrence of death due to adverse reaction to BNT166b2	Scenario 1: Maximum mortality from COVID-19 (same proportion of cases tested in 2023 applied to the total SARS cases of undefined cause, with a 50% reduction for the year 2024) versus minimum mortality from BNT166b2 (half the mortality rate measured in adolescents)	208,856	909,090	1:4
	Scenario 2: Minimum mortality from COVID-19 (calculated based only on cases with identification of a viral cause, with a 50% reduction for the year 2024) versus maximum mortality from BNT166b2 (same mortality rate as the population aged 16 or over)	548,246	42,373	13:1
Prevention of SARS due to COVID-19 versus occurrence of serious adverse event of special interest due to BNT166b2	Scenario 1: Considering the incidence of SARS due to COVID-19 equal to 10.2% of the total SARS cases reported in 2023 (highest incidence) versus the rate of adverse events equal to one-tenth of the rate observed in the population aged 16 or over (lower rate).	15,119	9901	2:1
	Scenario 2: Considering the incidence of SARS due to COVID-19 equal to the number of cases identified by PCR or viral antigen research (lower incidence) versus the rate of adverse events equal to that observed in the population aged 16 or over (higher rate).	39,863	990	40:1
Prevention of PIMS due to COVID-19 versus occurrence of serious adverse event of special interest due to BNT166b2	Scenario 1: Considering the incidence of COVID cases in children equal to the general population incidence, multiplied by one hundred (higher incidence—to correct for a notification rate of just 1%) versus the rate of adverse events equal to one-tenth of the rate observed in the population aged 16 or over (lower rate).	1,136,372	9901	115:1
	Scenario 2: Considering the incidence of COVID cases in children equal to the general population incidence, multiplied by one hundred (lower incidence to correct for a notification rate of only 10%) versus the rate of adverse events equal to that observed in the population aged 16 or over (higher rate).	11,363,644	990	11,000:1

Source: Calculated based on data from InfoGripe-OPENDATASUS,3 Fraiman *et al.* [7] Rosemblum *et al.* [8] Oudali *et al.* [9] Saied *et al.* [10].

4. Discussion

The benefit/risk ratio of the BNT162b2 mRNA vaccine can be inferred from two main factors: the incidence of severe cases due to COVID-19 in the population under analysis and the rate of mortality or serious adverse events associated with the product.

There is a margin of uncertainty in determining these two values in the pediatric population aged 6 months to 4 years. COVID-19 incidence and mortality decrease from 2022 to 2023 in Brazil, including this age group. Nevertheless, the difficulty in ascertaining the viral cause of SARS cases in which PCR tests or antigen research were not performed allows for a relatively wide range of variation to calculate the current COVID-19 incidence and mortality.

The determination of the rates of mortality and serious adverse events associated with the use of BNT162b2 in the population aged 6 months to 4 years is also uncertain due to the scarcity of large studies in this age group.

Regarding mortality associated with BNT162b2 in adults, it was observed that there were no differences between age-adjusted and unadjusted mortality rates, suggesting that age is not a determinant of different mortality patterns between vaccinated people and the general population.

Qualitatively, the profile of deaths reported as adverse events related to BNT162b2 differed from the general mortality of the population. A significant increase in the proportion of deaths due to cerebrovascular disease was observed, while deaths due to cancer and chronic respiratory disease were reported at a significantly lower rate compared to the general population [8]. This may occur only due to increased awareness on cardiovascular events in the vaccinated population, which is also probably the cause of the higher registry of deaths due to COVID-19 in this group. However, the biological plausibility of cardiovascular events due to vaccine and the increase in the proportion of deaths in the youngest group (16 - 17 years) in the vaccinated population, when compared to the general population (0.3% vs 0.1%, $p = 0.02$) suggests that a small but significant increase in the risk of death with BNT162b2 is real.

The rate of short-term adverse events is likely to be lower in children between 6 months to 4 years old than in adolescents. Periodic reports from the USA Centers for Disease Control have recorded only minor adverse effects in children, and until the most recent data (550,000 children who had already received the third booster dose), no deaths were recorded [14].

Thus, a reasonable conclusion is that adverse events to BNT162b2 are possible in children, but at much lower rates than in adults.

Because the incidence of COVID-19 is declining, the most likely current scenario seems to be one of transition, a situation in which the NNT/NNH ratio still favors the use of BNT162b2 mRNA, but going to a moment crossing a threshold for which the NNT/NNH ratio ceases to be favorable to the use of the product and its adverse effects begin to predominate. It should be noted that determining the exact moment at which this transition occurs is impossible with the existing data.

More importantly, it should be noted that the effect size of BNT162b2 in this pediatric population, both for good and for bad—prevention of severe COVID-19 cases or the occurrence of adverse effects—is quite small. This translates into very high NNT and NNH values. With the NNT varying between 250,000 and 500,000, the decision to make vaccination of the population aged 6 months to 4 years mandatory, affecting a large number of people (approximately 12 million children), would influence the outcome of COVID-19 mortality in approximately 30 to 50 children. With the NNH ranging between 50,000 and 900,000, the mortality due to adverse effect would affect between 20 to 200 children. As it is impossible to determine when one or the other (the benefit or the damage) will predominate, the decision to make vaccination mandatory in this age group becomes doubtful [15].

In this situation of very close values between potential benefit and risk, the obligation to comply with the complete vaccination schedule brings individual risks, as it treats all children in the same way, regardless of their clinical conditions. A child who is known to have contracted COVID-19 in recent months has little or no benefit from inoculation with the vaccine, but the risk of adverse events may persist. After the first dose of BNT162b2, another child who showed signs or symptoms of a serious adverse reaction may be at risk of a worse adverse reaction when receiving the second dose of the same product.

On the other hand, children who have not had recent contact with COVID-19 would probably have individual benefit, in the short term, from the protection provided by the vaccine.

Therefore, when assessing the short-term risks and benefits in the pediatric population, the current epidemiological situation indicates that the best public health policy is the free decision-making between healthcare professionals and users on an individual basis (including the choice of the kind of vaccine should be used) instead of mandatory vaccination.

In Hong Kong SAR, two types of vaccines are widely available (BNT162b2 mRNA and CoronaVac, the inactivated virus vaccine) and the population can choose from. In this scenario, two important studies were carried out: Wong *et al.* did not observe a quantitatively significant difference in mortality rates or short-term adverse effects between the two vaccines [16]. However, qualitatively, there were differences. The risk of carditis is not observed in CoronaVac but is present in BNT162b2 [17]. In addition to the possibility of the individual choosing of the product to be used for immunization, these results led to a policy in Hong Kong SAR of monitoring the occurrence of carditis after the first dose of BNT162b2 (if carditis is identified, CoronaVac is used for the second dose) [18]. These experiences point to the importance of specific assessment of the individual's clinical conditions and the possibility of opting for one or another available vaccine instead of the mandatory policy on the use of a single product in pediatric population.

In addition to the short-term effects, it is necessary to discuss the possibilities

of long-term risks associated with repeated mRNA use, which are currently unknown. Physicians are accustomed to the concept of DNA being transcribed into RNA, but they are usually not aware that there is a path in the opposite direction. Nevertheless, the retroposition of RNA into DNA (reverse transcription) also occurs in humans and can lead to the incorporation into the genome of material introduced in the form of exogenous RNA [2].

A single *in vitro* study demonstrated the incorporation of mRNA of BNT162b2 vaccine into human DNA [3]. Although this study has been criticized by comments that it does not confirm that BNT162b2 retroposition really occurs *in vivo* [19], it should be at least an alert for serious concern. There are still no published studies that investigated the risk of incorporation of the mRNA vaccine into human DNA *in vivo*.

The Ibero-Latin American Declaration on Ethics and Genetics establishes that "free and informed consent to carry out of genetic tests and interventions on the human genome must be guaranteed through appropriate bodies, especially in regard to children, incapacitated people and groups that require special protection" [20]. Thus, the wide communication of the best current information on benefits/risks of mRNA vaccination (including scientific doubts about the risks of RNA retroposition) along with the guarantee of free informed choice regarding the use or not of this new product seems to be the best public health policy.

In the early phases of the COVID-19 pandemic, it could be understood that the benefits of rapid control of viral transmission outweigh the potential risks of using mRNA, but current epidemiological data no longer support this position, especially for the pediatric population.

In conclusion, data presented here indicate that the short-term benefit/risk balance of the BNT162b2 mRNA in the age group from 6 months to 4 years in Brazil at the beginning of 2024 is borderline. Due to the lack of evidence of an obvious benefit in the short term and the possibility of future risks, it is argued that mandatory use of this still-new product in the pediatric age group should be reviewed; additionally, it may be suggested that vaccines based on traditional platforms should remain available until long-term safety results of mRNA vaccination become fully known.

Data Availability

All data files used in this research are publicly available and also may be obtained at request to the author.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Brasil Ministry of Health (2024) Nota Técnica 118/2023-CGICI/DPNI/SVSA/MS. https://www.gov.br/saude/pt-br/vacinacao/informes-e-notas-tecnicas/nota-tecnica-

no-118-2023-cgici-dpni-svsa-ms/view

[2] Domazet-Lošo, T. (2022) mRNA Vaccines: Why Is the Biology of Retroposition Ignored? *Genes*, **13**, Article 719. https://doi.org/10.3390/genes13050719

[3] Aldén, M., Olofsson Falla, F., Yang, D., Barghouth, M., Luan, C., Rasmussen, M., *et al.* (2022) Intracellular Reverse Transcription of Pfizer Biontech COVID-19 mRNA Vaccine BNT162b2 *in Vitro* in Human Liver Cell Line. *Current Issues in Molecular Biology*, **44**, 1115-1126. https://doi.org/10.3390/cimb44030073

[4] Brasil Ministry of Health (2024) SRAG 2021 a 2023—Incluindo dados da COVID-19. https://opendatasus.saude.gov.br/dataset/

[5] Brazilian Institute of Geography and Statistics (2024) Census Overview 2022. Age Piramid. https://censo2022.ibge.gov.br/panorama/?utm_source=ibge&utm_medium=home&utm_campaign=portal

[6] Muñoz, F.M., Sher, L.D., Sabharwal, C., Gurtman, A., Xu, X., Kitchin, N., *et al.* (2023) Evaluation of BNT162b2 Covid-19 Vaccine in Children Younger than 5 Years of Age. *New England Journal of Medicine*, **388**, 621-634. https://doi.org/10.1056/nejmoa2211031

[7] Fraiman, J., Erviti, J., Jones, M., Greenland, S., Whelan, P., Kaplan, R.M., *et al.* (2022) Serious Adverse Events of Special Interest Following mRNA COVID-19 Vaccination in Randomized Trials in Adults. *Vaccine*, **40**, 5798-5805. https://doi.org/10.1016/j.vaccine.2022.08.036

[8] Rosenblum, H.G., Gee, J., Liu, R., Marquez, P.L., Zhang, B., Strid, P., *et al.* (2022) Safety of mRNA Vaccines Administered during the Initial 6 Months of the US COVID-19 Vaccination Program: An Observational Study of Reports to the Vaccine Adverse Event Reporting System and V-Safe. *The Lancet Infectious Diseases*, **22**, 802-812. https://doi.org/10.1016/s1473-3099(22)00054-8

[9] Ouldali, N., Bagheri, H., Salvo, F., Antona, D., Pariente, A., Leblanc, C., *et al.* (2022) Hyper Inflammatory Syndrome Following COVID-19 mRNA Vaccine in Children: A National Post-Authorization Pharmacovigilance Study. *The Lancet Regional Health—Europe*, **17**, Article 100393. https://doi.org/10.1016/j.lanepe.2022.100393

[10] Hamad Saied, M., van der Griend, L., van Straalen, J.W., Wulffraat, N.M., Vastert, S. and Jansen, M.H.A. (2023) The Protective Effect of COVID-19 Vaccines on Developing Multisystem Inflammatory Syndrome in Children (MIS-C): A Systematic Literature Review and Meta-Analysis. *Pediatric Rheumatology*, **21**, Article No. 80. https://doi.org/10.1186/s12969-023-00848-1

[11] Brasil Ministry of Health (2024) COVID-19 No Brasil. https://infoms.saude.gov.br/extensions/covid-19_html/covid-19_html.html

[12] Prado, M.F.d., Antunes, B.B.d.P., Bastos, L.d.S.L., Peres, I.T., Silva, A.d.A.B.d., Dantas, L.F., *et al.* (2020) Analysis of COVID-19 Under-Reporting in Brazil. *Revista Brasileira de Terapia Intensiva*, **32**, 224-228. https://doi.org/10.5935/0103-507x.20200030

[13] CDC (2021) Deaths by Underlying Cause. https://wonder.cdc.gov

[14] Hause, A.M., Marquez, P., Zhang, B., Moro, P.L., Myers, T.R., Bradley, C., *et al.* (2023) Safety Monitoring of mRNA COVID-19 Vaccine Third Doses among Children Aged 6 Months-5 Years—United States, June 17, 2022–May 7, 2023. *Morbidity and Mortality Weekly Report*, **72**, 621-626. https://doi.org/10.15585/mmwr.mm7223a2

[15] Munro, A.P.S., Jones, C.E. and Faust, S.N. (2024) Vaccination against COVID-19—Risks and Benefits in Children. *European Journal of Pediatrics*, **183**, 1107-1112.

https://doi.org/10.1007/s00431-023-05380-8

[16] Wong, C.K.H., Lau, K.T.K., Xiong, X., Au, I.C.H., Lai, F.T.T., Wan, E.Y.F., *et al.* (2022) Adverse Events of Special Interest and Mortality Following Vaccination with mRNA (BNT162b2) and Inactivated (Coronavac) SARS-CoV-2 Vaccines in Hong Kong SAR: A Retrospective Study. *PLOS Medicine*, **19**, e1004018. https://doi.org/10.1371/journal.pmed.1004018

[17] Lai, F.T.T., Li, X., Peng, K., Huang, L., Ip, P., Tong, X., *et al.* (2022) Carditis after COVID-19 Vaccination with a Messenger RNA Vaccine and an Inactivated Virus Vaccine. *Annals of Internal Medicine*, **175**, 362-370. https://doi.org/10.7326/m21-3700

[18] Carleton, B.C., Salmon, D.A., Ip, P., Wong, I.C.K. and Lai, F.T.T. (2023) Benefits V. Risks of COVID-19 Vaccination: An Examination of Vaccination Policy Impact on the Occurrence of Myocarditis and Pericarditis. *The Lancet Regional Health— Western Pacific*, **37**, Article 100797. https://doi.org/10.1016/j.lanwpc.2023.100797

[19] Merchant, H.A. (2022) Comment on Aldén Et Al. Intracellular Reverse Transcription of Pfizer Biontech COVID-19 mRNA Vaccine BNT162b2 *in Vitro* in Human Liver Cell Line. *Current Issues in Molecular Biology*, **44**, 1661-1663. https://doi.org/10.3390/cimb44040113

[20] (2002) Declaration Ibero-Latin American on Ethics and Genetics. http://www.bioetica.org.br/?siteAcao=DiretrizesDeclaracoesIntegra&id=5