Can a microbiota-derived health supplement mitigate adverse events after COVID-19 vaccination in children?

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has caused a global pandemic with high rates of morbidity and mortality. Vaccination is effective in reducing the risk and severity of COVID-19; recent evidence suggests that gut microbiota have important effects on the immune response to vaccination.[1] Furthermore, there is increasing concern about adverse events associated with COVID-19 vaccines, which range from local inflammatory responses to anaphylactic reactions and thromboembolic events. Members of the phylum Bacteroidota are suspected to stimulate macrophages and monocytes to secrete a complex array of pro-inflammatory cytokines (eg, interferon-γ, tumour necrosis factor-α, and neurotoxins), which could trigger an aberrant immune response and contribute to a cytokine storm–induced abnormal inflammatory reaction.[2] Thus, the correction of gut dysbiosis through prebiotic/probiotic supplementation might offer a solution for the management of COVID-19 vaccine–related adverse reactions.

Exploration of a microbiota-derived health supplement

During the fifth wave of COVID-19 in Hong Kong, the Hong Kong SAR Government promoted the vaccination of children aged 6 months to 17 years. Because there is no prior information regarding the efficacy or safety of microbiota-derived health supplements in children undergoing COVID-19 vaccination, we performed a pilot study to evaluate the use of a health supplement available in Hong Kong, the G-NiiB Immunity formula (SIM01, containing 10 billion colony-forming units per sachet; developed by The Chinese University of Hong Kong), in alleviating adverse events after COVID-19 vaccination in children aged 5 to 17 years. Our primary objective was to investigate the safety of SIM01 in children after COVID-19 vaccination (first or second dose), when SIM01 use was initiated prior to vaccination and continued for 7 days after vaccination. We also evaluated the effects of SIM01 on rates of adverse events in vaccinated children, compared with historical data published by the vaccine manufacturers. We excluded children with a known history of COVID-19; a known chronic illness requiring long-term medication (ie, three standard doses per week); a known history of allergy to probiotics or prebiotics; a known history of lactose intolerance; a known history of (or active) infective endocarditis; and any use of other antibiotics, probiotics, or prebiotics during the study period. Each child's parents provided written informed consent to participate in the study.

The children received SIM01 (one sachet twice daily), beginning 1 week before the first dose of vaccine and continuing until 1 week after completion of the second dose of vaccine, or beginning 3 weeks before the second dose of vaccine and continuing until 1 week after vaccination; the supplementation protocol was determined by the vaccine dose that the participants received during the study period. Adverse events were recorded using a semi-structured adverse event assessment form that included 17 known paediatric adverse events after COVID-19 vaccination.[3,4] Additional symptoms and adverse event–related medical consultations were also recorded. The adverse events were assessed using the following four categories: none, minimal, tolerable, and distressing. Trained research personnel conducted phone interviews 1 week after vaccination to assess the effect of SIM01 on adverse event severity after COVID-19 vaccination, as well as adherence to the supplementation protocol. Participants received medical care for adverse events as needed. The demographic and medical characteristics of the participants were recorded, including the date of COVID-19 vaccination and type of vaccine received. Logistic regression was used to adjust for the effects of age, vaccine type, and vaccine dose on adverse events.

Adverse events with a microbiota-derived health supplement

Between April 2022 and August 2022, 102 children

aged 5 to 17 years were enrolled in the study. Seven children were excluded from analysis because they did not undergo vaccination or use SIM01. The remaining 95 children (mean age ± standard deviation [SD]=9.03 ± 3.123 years; 48.4% boys and 51.6% girls) used SIM01 supplementation while receiving at least one vaccine dose; they underwent assessments of adverse events. The supplementation protocol adherence rate was 97% across 124 vaccine doses. Notably, three participants reported temporary abdominal distension, loose stool, or mouth sores.

In terms of overall adverse events, the most common event was injection site symptoms (pain, induration and swelling, redness, itching, pruritus, and erythema) [Table]. The second most common event was fatigue/tiredness/lethargy or lack of energy/drowsiness. Other common adverse events were arm/leg pain and fever. BioNTech/Pfizer vaccine BNT162b2 has a higher rate of reported adverse events among children, compared with CoronaVac (Sinovac Biotech). The odds ratio (OR) for injection site symptoms was 2.59 (95% confidence interval [CI]=1.14-5.95; P=0.02) with BNT162b2. The ORs for arm/leg pain and fever were 6.5 (95% CI=1.44-60.89; P=0.08) and 13.78 (95% CI=2.22 to infinity; P=0.02), respectively. Other adverse event ORs were not statistically significant.

Thirty-eight children received the first dose of vaccine, whereas 86 received the second dose. Adverse events were similar between the two doses, although some effects were more common after the second dose: arm/leg pain (second dose: 18.6%, first dose: 10.5%), fever (12.8% vs 7.9%), chills (2.3% vs 0%), dizziness (5.8% vs 2.6%), headache (10.5% vs 0%), diarrhoea (4.7% vs 2.6%), fatigue (including fatigue/tiredness/lethargy or lack of energy/drowsiness; 26.7% vs 21.1%), chest discomfort (3.5% vs 0%), rhinorrhoea (2.3% vs 0%), and oropharyngeal pain (3.5% vs 0%). Most of these between-dose differences were not statistically significant; headache tended to be more common after the second dose (P=0.056).

Among the 95 evaluable participants, 81 were aged 5 to 12 years (mean ± SD=8.09 ± 2.24 years) and 14 were aged 13 to 17 years (mean ± SD=14.5 ± 1.40 years). Although the incidences of adverse events generally did not differ according to age, older children more frequently reported dizziness (OR=8.59, 95% CI=1.14-99.69; P=0.03) and headache (OR=9.05, 95% CI=1.80-61.98; P=0.005).

Adverse events without a microbiota-derived health supplement

The BNT162b2 Product Monograph showed that

TABLE. Overall adverse events after coronavirus disease 2019 (COVID-19) vaccination*

No.	Symptoms	Among all evaluable COVID-19 vaccine doses (n=124)			
		None	Minimal	Tolerable	Distressing
1	Injection site symptoms (pain, induration and swelling, redness, itching, pruritus, and erythema)	47 (37.9%)	59 (47.6%)	18 (14.5%)	0
2	Arm/leg pain	104 (83.9%)	17 (13.7%)	3 (2.4%)	0
3	Fever	110 (88.7%)	13 (10.5%)	1 (0.8%)	0
4	Chills	122 (98.4%)	2 (1.6%)	0	0
5	Dizziness	118 (95.2%)	4 (3.2%)	2 (1.6%)	0
6	Headache	115 (92.7%)	7 (5.6%)	2 (1.6%)	0
7	Nausea/vomiting	122 (98.4%)	1 (0.8%)	1 (0.8%)	0
8	Diarrhoea	119 (96.0%)	5 (4.0%)	0	0
9	Abdominal pain/abdominal distention	117 (94.4%)	5 (4.0%)	2 (1.6%)	0
10	Muscle pain/myalgia	124 (100%)	0	0	0
11	Joint pain	123 (99.2%)	1 (0.8%)	0	0
12	Fatigue/tiredness/lethargy or lack of energy/drowsiness	93 (75.0%)	28 (22.6%)	3 (2.4%)	0
13	Allergic reactions (eg, rash/itching)	117 (94.4%)	6 (4.8%)	1 (0.8%)	0
14	Chest discomfort	121 (97.6%)	3 (2.4%)	0	0
15	Rhinorrhoea	122 (98.4%)	2 (1.6%)	0	0
16	Oropharyngeal pain	121 (97.6%)	3 (2.4%)	0	0
17	Cough	124 (100%)	0	0	0

* Data are shown as No. (%)

the common adverse events among children aged 5 to 15 years are injection site pain or local reaction, tiredness, headache, chills, and myalgia.[3] Adverse events are more common in older children (aged 12 to 15 years). Children receiving SIM01 in our study had fewer adverse events when receiving BNT162b2, particularly regarding injection pain or local reaction (71% vs 84.3%-90.5% in Product Monograph data), tiredness (29% vs 51%-77%), headache (10% vs 38.2%-78.5%), chills (3% vs 12.4%-49.2%), and myalgia (0% vs 17.5%-42.2%). However, a direct comparison between our data and Product Monograph data could not be performed because there were considerable differences in study conditions. There was no obvious decrease in adverse events among children receiving CoronaVac, possibly because this vaccine has fewer adverse events.[5] A larger sample size may be necessary to identify any effect of SIM01 on adverse events after receipt of CoronaVac.

Implications and future work

Recent research indicates that baseline gut microbiota composition can predict immune responses to COVID-19 vaccines and vaccine-related adverse events in adults.[6,7] However, corresponding data for children have been limited. Our study showed that the microbiota-derived SIM01 formula is well tolerated in children aged 5 to 17 years. Among the 95 children in this study, only two discontinued SIM01 supplementation because of abdominal distension and loose stool or mouth sores. Most adverse events were mild and transient; none were considered distressing. Future studies should include a control group to validate the findings; they should also focus on mechanistic analyses. Our key findings were that SIM01 supplementation was safe for children before COVID-19 vaccination, and the rates of adverse events after vaccination appeared to be lower in children undergoing SIM01 supplementation than in a historical control group who did not use SIM01. These findings offer insights to support randomised controlled trials in the future, as well as information that may reduce vaccine hesitancy among parents and children.

Author contributions

Concept or design: CM Chow.
Acquisition of data: JYL Ching, PK Cheong.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: CM Chow, JYL Ching.
Critical revision of the manuscript for important intellectual content: J Hu, JYL Ching.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

CM Chow has disclosed no conflicts of interest. PK Cheong is an employee of GenieBiome Limited. J Hu is a scientist at GenieBiome Limited. JYL Ching is a clinical research consultant for GenieBiome Limited.

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Ethics approval

This study was approved by the GenieBiome Independent Review Board (Ref No.: GB-IRB 0001CT/2022) and was conducted in compliance with the Declaration of Helsinki. Written informed consent form was signed by the parent of all participants prior to study recruitment.

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