Second dose of COVID-19 vaccination in immediate reactions to the first BNT162b2

To the Editor,

Iatrogenic causes of anaphylaxis, such as by drugs and vaccines, can be fatal and are a major concern to the public.1–3 On the other hand, inappropriate apprehension toward the possibility of anaphylaxis may lead to COVID-19 vaccination delays or hesitancy, which are relevant impediments against achieving protective immunity for individuals and our community.3 Recently, Krantz and colleagues performed a retrospective analysis and observed that all adult patients were able to tolerate a second mRNA vaccine administration despite first-dose immediate anaphylactic hypersensitivity reactions.4 In Hong Kong (HK), Sinovac-CoronaVac and BNT162b2 have been approved for emergency use in ≥18-year-old and ≥12-year-old individuals, respectively.5 Indeed, as of 31 July 2021, there have been 4 cases of anaphylaxis (0.07 per 100,000) and 1 non-IgE anaphylaxis reaction (0.02 per 100,000) out of 5,663,200 injections.5 The current guidance states that people with previous severe allergic reactions to vaccines should not receive COVID-19 vaccination, unless advised by specialists in Immunology and Allergy.5 Our aim was to study the clinical tolerance of subsequent mRNA vaccination in children who developed immediate hypersensitivity reactions to their previous BNT162b2.

Pediatric patients who had hypersensitivity symptoms within 4 h after their first BNT162b2 were recruited into our prospective study (approved by the University of Hong Kong/HK West Cluster Institutional Review Board: UW21-157) after informed consent and assent.4 Trypsate from the initial acute reaction was unavailable at the time of the referrals. Basophil activation test (BAT) was performed according to instructions from Flow CAST® and reagent kits (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) as part of the research study to explore possible correlations between assay results and potential subsequent reactions during the rechallenge.6 Blood was incubated with a negative control, positive control (anti-IgE receptor antibody), PEG 2,000 (Sigma-Aldrich), and liposomal doxorubicin-PEG 2,000–3,500 complex separately in stimulation buffer.6 The activation marker, CD63, on basophils was measured by flow cytometry (Beckman Coulter Inc).6 The test was considered positive when CD63 expression was >5% according to the manufacturer's instructions and based on this criteria as the most common cutoff used for drug allergy workup.7–9 Skin testing was not performed due to its anaphylaxis-eliciting and accuracy concerns.10 After comprehensive counseling, legal guardians and patients were allowed to select between receiving their second dose of BNT162b2 by a graded approach (10%, or 0.03 mL of full dose, followed by 1-h close monitoring prior to the remainder 90%, or 0.27 mL, injection) or a single full-dose administration.2 All participants were observed for at least 1 h after each injection. The study protocol required their recording of no or any symptom in an electronic diary for 1 week.

Three participants who reported occasional rhinitis symptoms without any history of urticaria or other atopy were enrolled (Table 1). After their first BNT162b2 injection, generalized urticaria appeared within 1–3 h and lasted several days for 2 patients, whereas 1 patient continued to experience intermittent urticaria (Figure 1). BAT for participant 1 was indeterminant since this positive control was a non-responder (Table 1).6 He received his second BNT162b2 by the graded approach. A small wheal developed at his lower back 1 h afterward, which resolved 30 min after cetirizine. He had urticaria at his legs the next day and also intermittently for the next 17 days. BAT for the other 2 participants was negative, and 1 h of observation was uneventful after they received their second single full 0.3 mL BNT162b2 dose. Participant 2 complained of itchiness, which resolved after taking cetirizine. There was no moderate-to-severe reaction or serious adverse event reported in their diaries.
TABLE 1  Demographic characteristics and outcomes for the 3 participants

| Participants | Age (Yrs) | Sex | Ethnicity       | Medical history | Time to urticaria<sup>a</sup> | Duration of urticaria | Pre-dose 2 testing | Post-dose 2 1-h observation period | Post-dose 2 7-day electronic diary of symptoms | Pain at injection site | Fatigue | Urticaria | Itchiness | Headache |
|--------------|-----------|-----|-----------------|-----------------|-------------------------------|-----------------------|---------------------|-----------------------------------|-----------------------------------------------|----------------------|---------|-----------|-----------|---------|
| 1            | 12        | Male| Chinese         | Mild AR         | 1 h 15 min                    | 4 weeks               | Indeterminant       | 1 urticaria                       | Mild: days 0-3                  | Mild: day 0           | Mild: days 0-1 | None      | None     |
| 2            | 17        | Male| Chinese         | Mild AR         | 3 h                           | 3 days                | Negative            | Asymptomatic                   | Mild: days 0-2                  | Mild: days 0-2          | None             | Mild: day 0 | None      |
| 3            | 15        | Male| Chinese/Indian  | Mild AR         | 2 h 49 min                    | 10 days               | Negative            | Asymptomatic                   | Mild: days 0-2                  | Mild: days 1-2          | None             | None      | Mild: day 2|

Note: Definitions for severity of symptoms: mild = tolerable, not affecting daily activities, moderate = performance of some daily activities affected, severe: performance of some daily activities prevented.
Abbreviations: AR, allergic rhinitis; day 0, day of BNT162b2 administration; day 1, 1 day after BNT162b2 administration; Yrs, years.
<sup>a</sup>See Figure 1.
This is the first prospective study to demonstrate that children with immediate BNT162b2 first-dose reactions can safely receive their second injection according to the recommended immunization schedule without the need for premedication. Cutaneous symptoms persisted or recurred transiently after the second injection, which was successfully treated by oral an
antihistamine. Allergy evaluation by skin or basophil activation testing prior to receiving additional vaccine appeared to be clinically unnecessary and should be discouraged since it may cause vaccine delay or hesitancy. The cellular mechanisms underlying adverse reactions to mRNA vaccines and polyethylene glycol deserve further research.

KEYWORDS
allergy, BNT162b2, children, COVID-19, hypersensitivity, pediatric, vaccine

FUNDING INFORMATION
Health and Medical Research Fund, Grant/Award Number: COVID19F02

ACKNOWLEDGEMENTS
This work was supported by the research grant COVID19F02 from the Food and Health Bureau of the Government of Hong Kong. We thank Ms Heather Yeung at the Department of Pathology, Queen Mary Hospital (QMH), Hong Kong Special Administrative Region, China, and QMH pharmacist Ms Vivian Ngai for coordinating and conducting the basophil activation assay. We appreciate Dr Hon-Kuan Tong from QMH for his clinical care and monitoring of our patients after they received their vaccines.

CONFLICT OF INTEREST
Jaime S Rosa Duque, Daniel Leung, Elaine YL Au, and Yu-Lung Lau declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Jaime Sou Rosa Duque: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Funding acquisition (supporting); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Software (lead); Supervision (lead); Validation (lead); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead).
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REFERENCES
1. Poussel G, Tanno LK, Claverie C, et al. Fatal anaphylaxis in children in France: analysis of national data. Pediatr Allergy Immunol. 2018;29(1):101-104. https://doi.org/10.1111/pai.12828
2. Broyles AD, Banerji A, Barmettler S, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. J Allergy Clin Immunol Pract. 2020;8(9s):S16-S116. https://doi.org/10.1016/j.jaip.2020.08.006
3. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. N Engl J Med. 2021;384(7):643-649. https://doi.org/10.1056/NEJMr2035343
4. Krantz MS, Kwah JH, Stone CA, Jr., et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. JAMA Intern Med. 2021;e213779. https://doi.org/10.1001/jamainternmed.2021.3779. Epub ahead of print.
5. Department of Health, the Government of Hong Kong Safety Monitoring of COVID-19 vaccines in Hong Kong. https://www.drugoffice.gov.hk/epo/en/doc/Safety_Monitoring_of_COVID-19_Vaccines_in_Hong_Kong.pdf. Accessed October 8, 2021.
6. Troelnikov A, Perkins G, Yuson C, et al. Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in patients with PEG allergy. J Allergy Clin Immunol. 2021;148(1):91-95. https://doi.org/10.1016/j.jaci.2021.04.032
7. BÜHLMANN Laboratories AG. Flow CAST® Basophil Activation Test (BAT) Flow Cytometry. https://buhlmannlabs.com/wp-content/uploads/BUHLMANN-Flow-CAST_FK-CCR_IFU-CE_2012-08-17.pdf. Accessed October 8 2021.
8. Marraccini P, Pignatti P, Dapos Alcamo A, Salimbeni R, Consonni D. Basophil activation test application in drug hypersensitivity diagnosis: an empirical approach. *Int Arch Allergy Immunol*. 2018;177(2):160-166. https://doi.org/10.1159/000490116

9. Steiner M, Harrer A, Himly M. Basophil reactivity as biomarker in immediate drug hypersensitivity reactions-potential and limitations. *Front Pharmacol*. 2016;7:171. https://doi.org/10.3389/fphar.2016.00171

10. Sellaturay P, Nasser S, Ewan P. Polyethylene glycol-induced systemic allergic reactions (anaphylaxis). *J Allergy Clin Immunol Pract*. 2021;9(2):670-675. https://doi.org/10.1016/j.jaip.2020.09.029