



# Experience of the first 1127 COVID-19 Vaccine Allergy Safety patients in Hong Kong - Clinical outcomes, barriers to vaccination, and urgency for reform

Valerie Chiang, MBBS<sup>a</sup>, Sabrina Wing Shan Mok, MA, RD<sup>b</sup>, June King Chi Chan, MSc, RD<sup>b</sup>, Wai Yan Leung, MSc<sup>c</sup>, Carmen Tze Kwan Ho, MBBS (HK), FRCP (Edin, London), FHKCP, FHKAM (Medicine)<sup>c</sup>, Elaine Y. L. Au, MBBS, FHKAM (Medicine), FRCPA, FHKAM (Pathology), D (ABMLI)<sup>a</sup>, Chak Sing Lau, MBChB, MD (Hons), FRCP (Edin, Glasg, Lond), FHKCP, FHKAM (Medicine)<sup>c</sup>, Tak Hong Lee, MBBChir (Cantab), MD (Cantab), ScD (Cantab), MRCP (UK), MRCPATH, FRCP (Lond), FRCPATH, FHKCP<sup>b,1</sup> and Philip Hei Li, MB BS (HK), M Res (Med) (HK), PDipID (HK), MRCP (UK), FHKCP, FHKAM (Medicine)<sup>c,1\*</sup>

## ABSTRACT

**Introduction:** Hong Kong has had a low incidence of COVID-19 vaccine related anaphylaxis, partly due to its Vaccine Allergy Safety (VAS) guidelines for screening those at higher risk of COVID-19 vaccine-associated allergic reactions. We characterize the initial experience of the VAS clinics, as well as the impact of unnecessary referrals to the vaccination program.

**Methods:** All patients attending the VAS Clinics of the public and private health services between February and June 2021 were reviewed.

**Results:** Out of 1127 patients assessed at VAS clinics, 1102 (97.8%) patients were recommended for vaccination. Out of those contacted, more than 80% (450/558) received vaccination successfully; the remaining had not yet booked their vaccinations. The majority (87.5%) of patients not recommended was due to potential excipient allergies. Males were significantly more likely to be recommended (OR = 5.822, 95% CI = 1.361-24.903,  $p = 0.007$ ), but no other features were associated with recommendation for vaccination. Almost half (45.1%) of public service referrals were rejected due to insufficient information or incorrect indications for referral. The majority of cases (56.2%) of patients referred for suspected "anaphylaxis" did not fulfil diagnostic criteria.

**Discussion:** COVID-19 vaccination is very safe and 98% of high-risk patients were recommended for vaccination. Barriers to VAS include a high proportion of inappropriate referrals, inaccurate diagnoses of anaphylaxis and inability to diagnose excipient allergies. Our data validates that a prior history of COVID-vaccine unrelated anaphylaxis should be removed as a precaution for vaccination. Closer collaborations between primary care and allergy specialists and changes in pharmaceutical legislation should be made a priority to promote vaccination uptake.

<sup>a</sup>Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Hong Kong, China

\*Corresponding author. Department of Medicine, Queen Mary Hospital, The University of Hong Kong, 102 Pokfulam Road, Hong Kong, China  
E-mail: [liphilip@hku.hk](mailto:liphilip@hku.hk)

<sup>1</sup> These authors contributed equally to this work.

Full list of author information is available at the end of the article

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**Keywords:** COVID-19, Vaccine, Allergy, Hypersensitivity, Safety, Hong Kong, Anaphylaxis

## INTRODUCTION

Despite having one of the world's highest population densities, Hong Kong has successfully kept the spread of coronavirus disease 2019 (COVID-19) under control. In February 2021, Hong Kong started its territory-wide COVID-19 vaccination program, providing its citizens with 2 vaccine options: the Sinovac CoronaVac (SV) and Fosun Pharma BioNTech Comirnaty (BT).

The vaccination program is currently the most hopeful anti-COVID-19 strategy and is anticipated to finally instigate the end of the pandemic. Although vaccine-associated allergic reactions and anaphylaxis are extremely rare, even before the commencement of COVID-19 vaccinations in Hong Kong, the overall vaccine acceptance rate by the public was already lower than 40%.<sup>1,2</sup> This low acceptance rate was correlated with perceived harm of COVID-19 vaccination, as well as lack of trust in the healthcare system. Similar to other major cities, reports of suspected anaphylaxis and severe allergic reactions after COVID-19 vaccination rapidly dominated news reports, creating major safety concerns and vaccine hesitancy.

In light of this, the Hong Kong Institute of Allergy (HKIA) established a Vaccine Allergy Safety (VAS) task force and published the first set of consensus statements on the approach of COVID-19 VAS in April 2021.<sup>3</sup> The objectives of the statements were to define those people at higher risk of potential COVID-19 vaccine-associated allergies, and to highlight the importance of pre-vaccination and post-vaccination assessment by frontline healthcare workers and evaluation by specialists. The published precautions were in line with those set forth by the Department of Health (DH) of Hong Kong.<sup>4</sup> Individuals at higher risk of COVID-19 vaccine-associated allergic reactions were defined by: (1) suspected allergic reaction(s) to prior COVID-19 vaccination, (2) history of anaphylaxis, or (3) a history of severe, immediate-type allergic reactions to multiple foods or more than 1 class of drugs. Individuals meeting these criteria

were recommended to defer COVID-19 vaccination until physician assessment, and, if deemed necessary, to be referred for formal allergist assessment to exclude potential COVID-19 vaccine or excipient-associated allergies. Vaccination for COVID-19 vaccine-naïve patients was contraindicated in those whose potential excipient allergy could not be excluded. However, these interim recommendations were primarily based on expert consensus and not evidence based. Alike many countries, these recommendations are subject to continuous update as further evidence regarding COVID-19 VAS emerges.

The HKIA and DH guidance proved to be successful in maintaining a low rate of COVID-19 vaccine-associated allergies. As of June 2021, there have only been 4 confirmed cases of anaphylaxis (0.07 per 100,000 doses administered), a rate much lower than incidents recorded by other countries.<sup>5-8</sup> This low anaphylaxis rate has been essential to maintain vaccine confidence within the public and drive the target of achieving herd immunity.

That being said, there remains a balance between maintaining vaccine safety and promoting vaccine uptake. Compounded by a shortage of allergists in Hong Kong, both public and private allergy centers have received a compelling number of VAS referrals.<sup>9</sup> There have also been reports of unnecessary referrals or inappropriate deferrals of COVID-19 vaccinations against HKIA and DH guidance. It has been an overwhelming challenge to see and assess all referred patients in a timely manner, resulting in long waiting times and delays in vaccinations. Such barriers to vaccination would likely further aggravate the public's distrust in the local healthcare system. This led to the need for pre-vaccine clinic referral screening and rejection of inappropriate referrals (with either incorrect indications or insufficient information) in the public sector since June 2021. This is different in the private sector where many patients self-refer and there is much less triage undertaken. In order to continue promoting vaccine uptake, there is an

urgent need to assess whether update of the strategies regarding COVID-19 VAS in Hong Kong is required.

In this report, we characterize the initial experience of the first 1127 patients attending VAS clinics of both the public and private healthcare services in Hong Kong. We present the clinical outcomes, evaluate the clinical features associated with those deemed at higher risk of COVID-19 vaccine-associated allergic reactions (and therefore recommended to defer vaccination) as well as the impact of unnecessary referrals or inappropriate deferrals on our vaccination program. Finally, we present possible solutions to further enhance COVID-19 vaccine uptake and VAS assessment in the near future.

## METHODS

All available medical records of patients attending the public service run by the Hospital Authority Hong Kong West Cluster (HKWC) VAS Clinic (hereafter referred to as the "HKWC cohort") and private service run by the Hong Kong Sanatorium & Hospital for COVID-19 VAS (hereafter referred to as the "HKSH cohort") between February to June 2021 were reviewed. The HKWC and HKSH are the only public and private hospitals, respectively, with Specialists in Immunology & Allergy in Hong Kong; and likely represent the majority of patients undergoing COVID-19 VAS evaluation during the study period. This would also resolve any potential selection bias between public sector and private sector patients, as all patient records were captured and analysed.

Medical records from the HKWC and HKSH cohorts were reviewed with clinical data anonymously extracted. Only cases with complete medical records were analysed. Extracted clinical data included age, sex, indications for referral (suspected allergic reaction[s] to prior COVID-19 vaccination, history of drug/excipient allergy, or other), allergy investigations performed and outcome of allergist evaluation (if deemed at higher risk of COVID-19 vaccine-associated allergic reactions and whether to proceed with vaccination or not). Some patients had multiple indications for referral. For the HKWC cohort, additional information, including the overall

number of referrals (both accepted and rejected) as well as the presence of allergist-confirmed anaphylaxis and etiologies of anaphylaxis, was also available and extracted. Referrals were only accepted in the HKWC cohort if the reason for referral was consistent with the DH and HKIA guidance.

As per HKIA recommendations, patients with a prior history of suspected "anaphylaxis" were evaluated following the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) anaphylaxis criteria.<sup>10</sup> Severe, immediate-type allergic reaction was classified to be Grade II or above by Ring and Messmer grading.<sup>11</sup> Patients who never received any prior COVID-19 vaccination were categorized as "pre-vaccine", while those with suspected allergy to prior COVID-19 vaccination were categorized as "post-vaccine".

Allergy investigations were performed after initial allergist evaluation only if deemed clinically necessary. The most appropriate workup was selected for each patient on a case-by-case basis, depending on individual clinical history. *In vivo* investigations included allergy skin testing to index allergens (drugs and/or food), or excipients (such as polyethylene glycol [PEG]) when an excipient allergy was suspected. Both skin prick and intradermal skin tests were employed. For PEG, molecular weights of 2000, 3350, and 4000 Da, as well as various PEGylated drugs were used, as recommended by various publications.<sup>12,13</sup> Drug provocation tests were performed in cases of low pre-test probability to exclude drug allergies when clinically indicated. For post-vaccine patients with suspected immediate-type allergic reactions to prior COVID-19 vaccine, vaccine skin testing (with SV and BT) was also performed. *In vitro* tests included basophil activation tests (BAT), enzyme-linked immune absorbent spot and lymphocyte transformation tests to index drugs, excipients, and/or vaccines were performed for cases with a high pre-test probability of having an excipient or vaccine-associated allergy. All allergy skin and drug provocation tests were performed in accordance to the International Consensus on drug allergy.<sup>14,15</sup> All patients recommended for vaccination were interviewed (either via

telephone or in-person) for vaccination status update, at least 2 weeks after allergist consultation.

Categorical variables were expressed as numbers (percentages), and continuous variables were expressed as either mean (standard deviation) or median (range) when appropriate. Association analysis were used to identify associations between demographics/clinical features and suspected COVID-19 vaccine-associated allergic reactions. The chi-squared statistic and independent sample T-tests were used to compare categorical and continuous variables between groups in association analysis, respectively. A p-value of less than 0.05 was considered statistically significant. SPSS Statistics version 21 (IBM, Armonk, NY, USA) was used for all analysis. Data extraction was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

## RESULTS

### Above 97% patients could proceed with COVID-19 vaccination after allergist evaluation

Between February and June 2021, a total of 1127 patients underwent evaluation for COVID-19 VAS. Overall, the male:female ratio was 1:2 and the median age was 49 (range: 15-97) years. Only 26.1% of patients required allergy investigations (either *in vivo* or *in vitro*) after initial evaluation. After complete allergist evaluation, 1102 (97.8%) of all patients were deemed not to be clinically compatible with vaccine or excipient-associated allergies and were recommended to proceed with vaccination. Of the patients recommended for vaccination, we managed to contact half of them (558/1102). Out of these individuals, more than 80% (450/558) confirmed that they had received subsequent COVID-19 vaccination successfully. None reported any immediate-type allergic reactions afterwards. The remaining patients had not yet booked their vaccinations despite recommendation. Details and breakdown of the HKWC and HKSH cohorts are shown in [Table 1](#). The proportion of patients attending pre-vaccine VAS evaluation and recommended to defer COVID-19 vaccination (due to higher risk of COVID-19 vaccine-associated allergic reactions) is shown in [Fig. 1](#).

### Majority of patients recommended to defer COVID-19 vaccination were due to inability to exclude potential excipient allergies

Only 25 patients (24 pre-vaccine and 1 post-vaccine, 2.4%) were recommended to defer COVID-19 vaccination. Of these pre-vaccine patients, the majority (21 patients, 87.5%) were recommended to defer vaccination due to inability to confidently exclude possible excipient allergies based on prior history of multiple suspicious drug reactions. Excipient lists for implicated medications were not available for clarification due to Hong Kong's lack of mandatory disclosure of excipient lists. Two patients (8%) had positive skin tests to PEG and one patient (with both negative vaccine and excipient skin tests) had a positive BAT to PEG. One post-vaccine case was diagnosed with BT anaphylaxis and recommended to complete COVID-19 vaccination with SV as an alternative.

### Males were significantly more likely to be recommended for COVID-19 vaccination

Association analysis between patient demographics/clinical features and recommendation for vaccination (ie, not at higher risk for COVID-19 vaccine-associated allergic reactions) for pre-vaccine patients are shown in [Table 2](#). Male sex was associated with recommendation for vaccination (OR = 5.822, 95% CI = 1.361-24.903). None of the other demographic or clinical features reached statistical significance.

### Exponential increase in VAS referrals and high proportion of inappropriate referrals

The monthly number of referrals and patients seen, based on the HKWC pre- and post-vaccine subgroup, is shown in [Fig. 2](#). The HKWC VAS Clinic received a total of 3940 referrals during the study period (March 2021: 94, April 2021: 232, May 2021: 1100, June 2021: 2514) Due to limitation of manpower, only 587 (14.9%) of patients were seen during the study period. After commencement of pre-clinic referral screening in June 2021, 1133 out of 2514 (45.1%) of referrals were identified as inappropriate due to insufficient information or incorrect indications for referral.

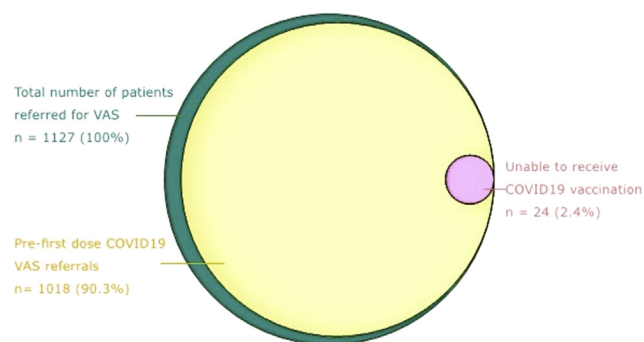
	HKWC cohort	HKSH Cohort	Combined cohort
Total patients seen	587	540	1127
Male sex	195 (33.2%)	184 (34.1%)	379 (33.6%)
Median age (range)	49 (18-97)	48 (15-90)	49 (15-97)
<b>Pre-vaccine referrals</b>	478 (81.4%)	540 (100%)	1018 (90.3%)
- History of suspected anaphylaxis	178 (37.2%)	45 (8.3%)	223 (19.8%)
- Suspected drug/excipient allergies	209 (43.7%)	309 (57.2%)	518 (50.9%)
Underwent allergy workup	91 (19.0%)	175 (32.4%)	266 (26.1%)
Recommended vaccination	475 (99.4%)	519 (96.1%)	994 (97.6%)
- Managed to contact after consultation	180 (41.4%)	290 (55.9%)	470 (47.3%)
- Of those contacted, received vaccination after recommendation	152 (84.4%)	235 (81.0%)	387 (82.3%)
<b>Post-vaccine referrals</b>	109 (18.6%)	-	-
- BioNTech Comirnaty	56 (51.4%)	-	-
- SinoVac CoronaVac	53 (48.6%)	-	-
Recommended vaccination	108 (99.1%)	-	-
- Managed to contact after consultation	88 (81.5%)	-	-
- Of those contacted, received vaccination after recommendation	63 (71.6%)	-	-
<b>Total: Recommended vaccination</b>	583 (99.3%)	519 (96.1%)	1102 (97.8%)
- Managed to contact after consultation	268 (46.0%)	290 (55.9%)	558 (50.6%)
- Of those contacted, received vaccination after recommendation	215 (80.2%)	235 (81.0%)	450 (80.6%)

**Table 1.** Demographics and clinical features of patients referred to both HKWC and HKSH VAS clinics for pre- and post-vaccine precautions

### Majority of referred patients with history of “anaphylaxis” did not meet anaphylaxis criteria after allergist review

In the HKWC subgroup, although 178 (37.2%) of all pre-vaccine referrals were for history of suspected “anaphylaxis”, only 78 patients (43.8%) were deemed to fulfil anaphylaxis diagnostic

criteria following allergist review, in accordance with the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) anaphylaxis criteria<sup>10</sup> For patients with confirmed anaphylaxis, the most common etiology of anaphylaxis was exercise induced anaphylaxis (EIA) or food-dependent EIA (20%). Breakdown of all allergist-confirmed etiologies of all anaphylaxis referrals (HKWC cohort) are shown in Fig. 3.



**Fig. 1** Venn diagram of patients attending for pre-vaccine precautions and recommended to defer vaccination

## DISCUSSION

We present the first study on COVID-19 VAS by reporting the clinical features associated with suspected COVID-19 vaccine or excipient-associated allergic reactions, as well as the impact of inappropriate referrals and the role of allergists on the COVID-19 vaccination program.

	Pre-vaccine assessment for COVID-19 Vaccine Allergy Safety (n=1018)		p-value
	Recommended for vaccination (n=994)	Recommended to defer vaccination (n=24)	
Male sex	344 (34.6%)	2 (8.3%)	0.007
Age (mean years ± SD)	50.0 ± 14.8	46.8 ± 13.6	0.293
<u>Pre-vaccine precautions</u>			
- History of suspected anaphylaxis	215 (21.6%)	8 (33.3%)	0.171
- Suspected drug allergy	502 (50.5%)	16 (66.7%)	0.118
- Other precautions <sup>a</sup>	291 (29.3%)	4 (16.7%)	0.178
History of chronic spontaneous urticaria	141 (14.2%)	5 (20.8%)	0.359

**Table 2.** Association analysis of factors associated with recommendation for COVID-19 vaccination in pre-vaccine patients. <sup>a</sup>Other precautions: e.g. suspected immediate-type and severe allergies to multiple foods, uncertain excipient allergies, idiopathic anaphylaxis etc

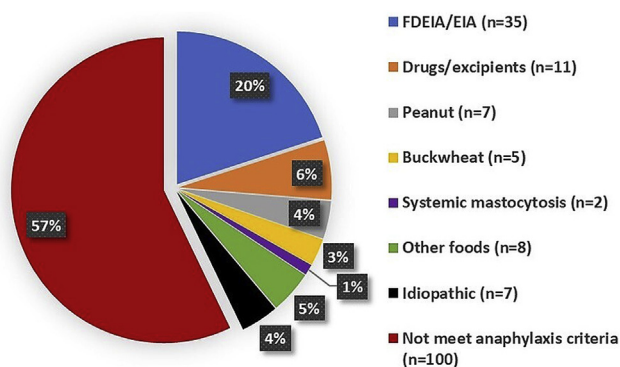
COVID-19 vaccination has proven to be very safe, with only 4 cases of anaphylaxis (0.07 per 100,000 doses administered) in Hong Kong so far.<sup>5</sup> This rate of COVID-19 vaccine-associated anaphylaxis is much lower than other countries such as the United States. Even out of the 1127 patients who were deemed at higher risk of COVID-19 vaccine-associated allergic reactions and referred for allergist review, only 2% of these patients were recommended to defer COVID-19 vaccination. The majority of those who were not approved for vaccination were those whose suspected potential excipient allergies could not be excluded. We managed to contact half of the

patients recommended for COVID-19 vaccination, of which more than 80% confirmed that they had received subsequent vaccination safely, with no reported immediate-type allergic reactions. The remaining have yet to book their vaccinations, despite recommendation.

Association analysis revealed that males were significantly more likely to be recommended for COVID-19 vaccination (ie, females were associated with suspected COVID-19 vaccine or excipient-associated allergies). A female predominance for suspected drug allergies has been well reported, including in our previous beta-lactam allergy study



**Fig. 2** Monthly number of referrals accepted, referrals rejected and patients seen at HKWC VAS Clinic from March to June 2021



**Fig. 3** Allergist-confirmed etiologies of confirmed and suspected anaphylaxis referrals seen at HKWC VAS Clinic (n = 178)

in Hong Kong.<sup>16-18</sup> However, our previous study suggested that sex may only be associated with allergy labelling, rather than genuine allergy per se.<sup>16</sup> As most pre-vaccine patients did not undergo confirmatory provocation tests (diagnoses mostly based on clinical history and skin tests only), this phenomenon may also hold true for COVID-19 vaccine or excipient-associated allergies, and will be investigated in future studies.

Aside from sex, we did not identify other demographic or clinical features associated with risk of COVID-19 vaccine or excipient-associated allergic reactions. Notably, there was no association between having a prior history of suspected anaphylaxis nor history of multiple drug allergies with recommendation for COVID-19 vaccination. This lack of association held true even after subgroup analysis selecting patients with allergist-confirmed anaphylaxis only (data not shown). Our findings concur with recent updates in other international guidelines. For example, both the United Kingdom's Medicines and Healthcare Products Regulatory Agency and Singapore's Ministry of Health have removed anaphylaxis to non-COVID-19 vaccine or associated excipients as contraindications to COVID-19 vaccination in their most recent recommendations.<sup>19-21</sup> With strongly supportive data, we also recommend that history of anaphylaxis (to non-COVID-19 vaccine or related excipients) should be removed as a precaution to COVID-19 vaccination.

History of multiple drug allergies has also been removed as a precaution or contraindication from many COVID-19 vaccine recommendations. Most authorities now recommend that only individuals with an allergic reaction to the first dose of the

vaccine, or with a known allergy to any component of the vaccines should be excluded from vaccination.<sup>22-24</sup> However, this sole exclusion criterion remains impractical in Hong Kong due to deficiencies in our pharmaceutical legislation.<sup>25</sup> Registered drugs in Hong Kong are still not mandated to include excipient lists in product inserts. In the absence of this information, excipient allergies remain almost impossible to diagnose.

This poses a challenge to recommend further vaccination if we are unable to exclude allergy to specific vaccine components, specifically PEG for BT. Excipients contained in SV have limited evidence to elicit potential allergic reactions. The excipient lists of both vaccines are shown in [Supplementary Table 1](#).<sup>26,27</sup> Furthermore, patients with potential undiagnosed excipient allergies undergo regular allergist review for further testing and are counselled accordingly. In order to avoid accidental re-exposure to the culprit excipient, patients are recommended to avoid empirically any new parenteral medications, especially medications with potentially cross-reactive or unlisted excipients, until a formal culprit can be identified.

As of July 21, 2021, only 30.7% of the eligible population in HK had been vaccinated. The COVID-19 VAS clinics were established to enhance vaccine uptake for individuals deemed at higher risk for COVID-19 vaccine-associated allergic reactions. However, the demand for this specialist service has proven to be overwhelming in both the public and private healthcare sectors. For the single HKWC VAS Clinic, there were more than 2500 referral letters received in June 2021 alone (greater than 25 times increase compared to March 2021).

Despite continuous medical education to primary care and family physicians, almost half of the screened referrals were ultimately rejected due to inappropriate reasons (not meeting DH and HKIA guidelines) for VAS clinic referral. Even more alarmingly, our HKWC subgroup analysis revealed that most patients referred for suspected history of "anaphylaxis" did not meet the criteria of anaphylaxis. The etiologies of the HKWC cases which fulfilled anaphylaxis criteria were consistent with our previous reports of anaphylaxis in Hong Kong, with a high proportion of EIA or food-dependent EIA.<sup>28,29</sup> Extrapolating inappropriate referrals and incorrect diagnoses of anaphylaxis alone, more than half of all patients referred VAS

clinic in June 2021 could have been directly vaccinated without need for prior allergist evaluation. The step of risk-stratification and prevention of unnecessary delays in vaccination heavily depends on the physicians initially evaluating a patient's allergy history and there is an important role for primary care and family physicians to conduct an initial triage based on objective clinical criteria provided by the DH and HKIA recommendations. In this regard, there is an unmet need to promote interdisciplinary collaboration in allergy services between primary care and specialists.

Evaluating our experience with COVID-19 VAS enabled us to identify some barriers to vaccination as well as potential areas for improvement. We also hope the evidence-based conclusions from this study will guide subsequent updates to recommendations and contraindications for vaccination for COVID-19 vaccination in Hong Kong. There is a clear urgency to reform our current workflow of suspected COVID-19 vaccine-associated allergies, from precautions during pre-vaccination screening to changes in medical infrastructure. We propose 3 important solutions to relieve the burden of unnecessary VAS referrals. First, we recommend updating the current HKIA and DH guidance to remove anaphylaxis as a precaution for COVID-19 vaccination as our data does not validate that a prior history of COVID-19 vaccine unrelated anaphylaxis alone is associated with higher risk of COVID-19 vaccine-associated allergic reactions. Thus only a history of COVID-19 vaccine-associated anaphylaxis should be kept as a precaution. Second, there should be closer collaborations between primary care and allergy specialists with a focus on improving allergy training for front-line doctors. In most cases, family and primary care physicians should be able to evaluate independently COVID-19 VAS and safeguard the vaccination program. This could then focus scarce specialist resources for use in patients at genuine higher risk of COVID-19 vaccine allergy. Specialist-nurse led or telecommunication clinics to screen the appropriateness of referrals or conducting pre-consultation assessments may also help in reducing unnecessary vaccine deferrals. These inter-disciplinary initiatives would also provide important patient counselling regarding VAS and encourage vaccination uptake, especially for

those who remain unwilling to receive vaccination despite lack of contraindications. Lastly, we echo the HKIA consensus statement and implore that full excipient lists for all registered drugs should be mandated in Hong Kong as soon as possible.<sup>3</sup> In the interim, a comprehensive list of potentially cross-reactive formulations of drugs containing common excipients to COVID-19 vaccines should also be made readily accessible for cross-referencing by healthcare professionals.

Boosting COVID-19 vaccination coverage is a priority for all countries and populations. It is imperative that allergy patients should not be excluded from vaccination for unproven justifications and not to be diagnosed incorrectly with excipient allergies. It is equally important that the public maintains confidence in vaccination safety. Appropriate VAS guidance is important to maintain low anaphylaxis rates but this requires continuous updating of guidelines as new evidence emerges, so that patients will be encouraged to undergo vaccination and the community can achieve herd immunity.

#### Abbreviations

BAT = basophil activation tests; BT = Fosun Pharma BioNTech Comirnaty; COVID-19 = coronavirus disease 2019; DH = Department of Health; HKIA = Hong Kong Institute of Allergy; NIAID/FAAN = National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network; PEG = polyethylene glycol; SV = Sinovac CoronaVac; VAS = Vaccine Allergy Safety.

#### Authors contribution

VC, SWSM, JKCC, WYL, CTKH, EYLA collected the data. VC, CSL, THL, PHL analysed and interpreted the data. All authors contributed in the writing and revision of the article.

#### Consent for publication

All authors consent for publication.

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#### Ethics approval

Approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

#### Availability of data and material

Not applicable.



**Declaration of competing interest**

The authors report no competing interests.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2021.100622>.

**Author details**

<sup>a</sup>Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Hong Kong, China.

<sup>b</sup>Allergy Centre, Hong Kong Sanatorium and Hospital, Hong Kong, China. <sup>c</sup>Division of Rheumatology & Clinical Immunology, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China.

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