

Impact of COVID-19 vaccines on thyroid function and autoimmunity and impact of thyroid autoimmunity on antibody response

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## Abstract

**Objectives:** We evaluated impact of COVID-19 vaccination on thyroid function and antibodies, and influence of pre-existing thyroid autoimmunity on neutralizing antibody (NAb) responses.

**Methods:** Adults without history of COVID-19/thyroid disorders who received COVID-19 vaccination during June–August 2021 were recruited. All received two doses of vaccines. Thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies were measured at baseline and 8 weeks post-vaccination. NAb against SARS-CoV-2 receptor-binding domain was measured.

**Results:** 215 individuals were included (129[60%] BNT162b2; 86[40%] CoronaVac recipients): mean age 49.6 years, 37.2% men, and 12.1% anti-TPO/Tg positive at baseline. After vaccination, TSH did not change ( $p=0.225$ ), but fT4 slightly increased (from  $12.0\pm 1.1$  to  $12.2\pm 1.2$  pmol/L [from  $0.93\pm 0.09$  to  $0.95\pm 0.09$  ng/dL],  $p<0.001$ ) and fT3 slightly decreased (from  $4.1\pm 0.4$  to  $4.0\pm 0.4$  pmol/L [from  $2.67\pm 0.26$  to  $2.60\pm 0.26$  pg/mL],  $p<0.001$ ). Only 3 patients (1.4%) had abnormal thyroid function post-vaccination, none clinically overt. Anti-TPO and anti-Tg titres increased modestly after vaccination ( $p<0.001$ ), without significant changes in anti-TPO/Tg positivity. Changes in thyroid function and anti-thyroid antibodies were consistent between BNT162b2 and CoronaVac recipients, except for greater anti-TPO titre rise post-BNT162b2 ( $p<0.001$ ). NAb responses were similar between individuals with and without pre-existing thyroid autoimmunity ( $p=0.855$ ).

**Conclusion:** COVID-19 vaccination was associated with modest increase in anti-thyroid antibody titres. Anti-TPO increase was greater among BNT162b2 recipients. However, there was no clinically significant thyroid dysfunction post-vaccination. NAb responses were not influenced by pre-existing thyroid autoimmunity. Our results provided important reassurance for people to receive COVID-19 vaccination.

**Keywords:** COVID-19; SARS-CoV-2; vaccines; thyroid function tests; autoimmunity

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has infected more than 480 million globally, leading to more than 6 million deaths. (1) COVID-19 is associated with multiple extra-pulmonary manifestations, including thyroid dysfunction. (2) Angiotensin-converting enzyme 2, the entry receptor for SARS-CoV-2, is found to be expressed in many organs, including the thyroid gland, (3) providing a mechanistic link between COVID-19 and thyroid dysfunction. In addition, case reports of Graves' disease and Hashimoto's thyroiditis after acute COVID-19 have raised concerns regarding SARS-CoV-2's potential in triggering thyroid autoimmunity. (4)

There are similar concerns for COVID-19 vaccination in triggering thyroid autoimmunity and causing thyroid dysfunction. The earliest case report in May 2021 described two patients without known thyroid disorder who developed Graves' disease a few days after receiving the Pfizer-BioNTech mRNA COVID-19 vaccine. (5) Following these cases, there was a report of a patient who developed thyroiditis around 2 weeks after Pfizer-BioNTech mRNA COVID-19 vaccination. (6) Since then, there are more than 80 cases of thyroid dysfunction following COVID-19 vaccination. (7) One postulated mechanism is 'autoimmune/inflammatory syndrome induced by adjuvants' (ASIA). (8) For example, the aluminium hydroxide as the adjuvant of CoronaVac may be the culprit of inducing subacute thyroiditis as post-vaccination ASIA. (9) Molecular mimicry is another postulated mechanism: SARS-CoV-2 spike protein, nucleoprotein, and membrane protein all cross-reacted with thyroid peroxidase (TPO), suggesting that anti-SARS-CoV-2 antibodies may promote autoimmune thyroiditis. (10) Furthermore, differences exist in the target antigens and types and intensities of immune responses with different SARS-CoV-2 vaccines. (11) BNT162b2 is the first mRNA vaccine widely used in human. By stimulating dendritic cells' maturation and eliciting robust T and B cell responses, RNA-based vaccines may activate bystander autoreactive lymphocytes. Hence, there is a theoretical concern

that the mRNA vaccine may reactivate autoimmune diseases. (12) It remains to be elucidated regarding the potential of different SARS-CoV-2 vaccines in altering thyroid function and autoimmunity.

Data on the impact of pre-existing thyroid autoimmunity on the efficacy of COVID-19 vaccination are limited. Although some vaccine trials have included patients with autoimmune disorders, (13) this group of patients was the minority and the nature of the autoimmune disorders was not necessarily thyroid-specific. Based on these trials, professional bodies such as the European Society of Endocrinology have issued statements suggesting that patients with stable endocrine disorders, including thyroid disorders, should follow the same recommendations as for the general population and receive COVID-19 vaccination accordingly. (14)

Currently available vaccines in Hong Kong include the mRNA vaccine (BNT162b2) and the inactivated virus vaccine (CoronaVac). To clarify these concerns, we prospectively evaluated (i) the anti-thyroid antibody titres and thyroid function among recipients of BNT162b2 and CoronaVac, and (ii) NAb responses between individuals with and without pre-existing thyroid autoimmunity.

## **Methods**

We performed a prospective follow-up study of COVID-19 vaccine recipients. Adults (age  $\geq 18$  years) who attended one of the three vaccination centres in the Hong Kong West Cluster (Sun Yat Sen Memorial Park Sports Centre, Queen Mary Hospital Staff Clinic and Sai Ying Pun Jockey Club General Out-patient Clinic) for COVID-19 vaccination between 14 June 2021 and 8 August 2021 were invited to participate in this study. Exclusion criteria included (i) history of COVID-19, (ii) history of

pituitary/thyroid disorders, (iii) use of thyroid hormone replacement or anti-thyroid medications, (iv) use of medications with potential interference with thyroid function, including glucocorticoids, amiodarone and anti-epileptic agents, (v) pregnancy, and (vi) abnormal thyroid function tests (TFTs) upon baseline blood tests.

All participants had baseline blood tests before the first dose of COVID-19 vaccine. Demographics and information on major cardiometabolic comorbidities were collected by participants' self-report at the time of vaccination. Diabetes was defined by the use of anti-diabetic medications or HbA1c  $\geq 6.5\%$  checked at baseline. Obesity was defined by body mass index  $\geq 27.5 \text{ kg/m}^2$ . All participants completed the two doses of COVID-19 vaccines according to the recommended schedule: 2 doses of CoronaVac administered 28 days apart; and 2 doses of BNT162b2 administered 21 days apart. At 8 weeks after baseline, these participants returned for the second set of blood tests.

For both sets of blood, serum thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were measured using Abbott Alinity i TSH, Free T4 and Free T3 chemiluminescent microparticle immunoassay (CMIA), respectively. The reference ranges for TSH, fT4 and fT3 were 0.35–4.94 mIU/L (0.35–4.94 uIU/mL), 9.01–19.05 pmol/L (0.70–1.48 ng/dL) and 2.43–6.01 pmol/L (1.58–3.91 pg/mL), respectively. The coefficients of variation (CV) of TSH, fT4 and fT3 assays were 1.5–2.1%, 2.0–3.1% and 2.4–4.8%, respectively. fT3/fT4 ratio (using pmol/L) was calculated as the indirect index of deiodinase activity. Abnormal TFTs were classified as (i) overt thyrotoxicosis when TSH  $< 0.35$  mIU/L (0.35 uIU/mL) and fT4  $> 19.05$  pmol/L (1.48 ng/dL); (ii) subclinical thyrotoxicosis when TSH  $< 0.35$  mIU/L (0.35 uIU/mL) but fT4 and fT3 were normal; (iii) overt hypothyroidism when TSH  $> 4.94$  mIU/L (4.94 uIU/mL) and fT4  $< 9.01$  pmol/L (0.70 ng/dL); and (iv) subclinical hypothyroidism when TSH  $> 4.94$  mIU/L (4.94 uIU/mL) but fT4 and fT3 were normal.

Quantitative measurements of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) titres were performed with Cobas Elecsys anti-TPO (RRID:AB\_2916057, [https://scicrunch.org/resolver/AB\\_2916057](https://scicrunch.org/resolver/AB_2916057)) and anti-Tg (RRID:AB\_2894922, [https://scicrunch.org/resolver/AB\\_2894922](https://scicrunch.org/resolver/AB_2894922)) electrochemiluminescence immunoassays, respectively. The CV were 2.5–7.0% and 4.6–5.6%, respectively. Positive anti-TPO and anti-Tg was defined by >34.0 IU/mL and >115.0 IU/mL respectively. Individuals with positive anti-TPO or anti-Tg at baseline were considered to have evidence of pre-existing thyroid autoimmunity. C-reactive protein (CRP) was measured with Abbott Alinity c CRP Vario assay. Elevated CRP was defined by  $\geq 5.0$  mg/L.

Neutralising antibody (NAb) against SARS-CoV-2 receptor-binding domain (RBD) was measured with the new version of the iFlash-2019-nCoV NAb kit, a one-step competitive chemiluminescence immunoassay on the iFlash 1800 analyzer (Shenzhen YHLO Biotech Co., Ltd., Shenzhen, China) according to the manufacturer's instructions. (15) The cut-off value for seropositivity was 15 AU/mL, and the maximum measurable value was 800 AU/mL. Values <9 AU/mL were considered 'negative'. Values between >9 and <15 were considered to be 'indeterminate'.

#### Study outcomes

The primary outcome was the absolute change in anti-TPO and anti-Tg titres after vaccination.

There were several secondary outcomes:

- (i) The absolute change in TSH, fT4 and fT3 levels post-vaccination;
- (ii) Differences, if any, in the changes in TFT and anti-thyroid antibody titres post-vaccination between the two types of vaccines;

- (iii) The TFT changes post-vaccination according to pre-existing thyroid autoimmunity;
- (iv) The influence of age and sex on the changes in TFT and anti-thyroid antibody titres post-vaccination; and
- (v) The relationship between pre-existing thyroid autoimmunity and NAb response.

This study has been approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 21-214), and written informed consent was obtained from all participants.

#### Statistical analyses

All statistical analyses were performed with IBM® SPSS® version 26. Two-sided p-values <0.05 were considered statistically significant.

Data were presented as mean ± standard deviation, median with interquartile range (IQR) or number with percentage as appropriate. Values not normally distributed were logarithmically transformed before analyses.

The baseline characteristics of BNT162b2 and CoronaVac recipients were compared using independent t-test for continuous variables and Chi-square/Fisher's exact test for categorical variables. Comparisons of anti-thyroid antibody titres and TFTs before and after COVID-19 vaccination were performed using paired t-test. Comparisons of anti-TPO/Tg positivity before and after COVID-19 vaccination were performed using McNemar's test. Comparisons of the changes in

TFTs and anti-thyroid antibody titres post-vaccination between BNT162b2 and CoronaVac recipients were performed using independent t-test. Comparisons of the changes in TFTs post-vaccination between individuals with and without pre-existing thyroid autoimmunity were performed using independent t-test. Pearson correlation was used to evaluate the correlations of age with various TFT and anti-thyroid antibody parameters. Comparisons of the changes in TFTs and anti-thyroid antibody titres post-vaccination between men and women were performed using independent t-test. NAb response among vaccine recipients with and without pre-existing thyroid autoimmunity was compared using Chi-square test. Pearson correlation was used to evaluate the correlations between NAb titres and anti-thyroid antibody titres.

#### Sample size calculation

At the time of designing the study, there was no study in the literature regarding the impact of COVID-19 vaccination on thyroid autoimmunity. Hence, the sample size of our study was estimated based on the results from our prospective follow-up of thyroid function and autoimmunity among COVID-19 survivors, representing the changes after natural infection by SARS-CoV-2. The details of subject recruitment were described in our previous publication. (2) We evaluated a cohort of 179 adults without known thyroid disorder who were admitted to Queen Mary Hospital (a major COVID-19 centre) for confirmed COVID-19 from 21 July 2020 to 20 January 2021, and had thyroid function tests and anti-thyroid antibodies measured both on admission and at 3-month follow-up. Upon 3-month follow-up, there was an increase in the mean natural logarithmic titre values of anti-TPO by  $0.0973 \pm 0.449$  ( $p < 0.001$ ), and the mean natural logarithmic titre values of anti-Tg by  $0.0933 \pm 0.428$  ( $p < 0.001$ ). Based on these results, our study would require 170 subjects to achieve a power of 80% and two-sided significance of 5% to detect the difference. In anticipation of up to 20% loss to follow-up, we therefore planned to include 200 subjects in this study.



## Results

### Baseline characteristics

In total, 222 individuals agreed to participate in this study. Seven individuals had abnormal baseline TFTs and were excluded: six had subclinical thyrotoxicosis and one had isolated mildly elevated fT3. Their evolution of TFTs is summarised in **Table 1**. All seven patients completed the two doses of COVID-19 vaccines without worsening in thyroid function.

Hence, 215 individuals (all with normal baseline TSH, fT4 and fT3) were included in this analysis (129 BNT162b2 recipients [60%]; 86 CoronaVac recipients [40%]). Their characteristics are summarised in **Table 2**. All patients received the same vaccine for both doses. Mean age was  $49.6 \pm 12.5$  years, with 37.2% men. Except for older age among CoronaVac recipients, baseline characteristics (including TFTs and anti-thyroid antibodies) were comparable between the two groups. Overall, 26 individuals (12.1%) were positive for anti-TPO/anti-Tg at baseline, suggestive of pre-existing thyroid autoimmunity.

### Changes in anti-thyroid antibody titres and TFTs post-vaccination (**Table 3**)

Regarding the primary outcome of our study, we observed statistically significant, though modest, increases in anti-TPO (from 7.50 [IQR: 5.90–11.2] to 9.80 IU/mL [IQR: 7.80–13.1],  $p < 0.001$ ) and anti-Tg (from 12.4 [IQR: 11.1–14.9] to 15.7 IU/mL [IQR: 14.2–18.2],  $p < 0.001$ ) titres post-vaccination. The power ultimately achieved for this primary outcome was 99%.

Two recipients had incident anti-TPO positivity (anti-TPO rose from 25.9 to 34.2 IU/mL; and from 23.8 to 41.3 IU/mL respectively; both being CoronaVac recipients): both had normal TFTs post-

vaccination. All recipients with baseline anti-TPO positivity remained anti-TPO positive post-vaccination. Overall, there was no change in anti-TPO positivity post-vaccination ( $p=0.500$ ). There was no change in anti-Tg positivity post-vaccination overall or in either group.

Regarding TFTs, TSH levels did not change after vaccination ( $p=0.225$ ). fT4 showed a statistically significant increase (from  $12.0\pm 1.1$  to  $12.2\pm 1.2$  pmol/L [ $0.93\pm 0.09$  to  $0.95\pm 0.09$  ng/dL],  $p<0.001$ ), while fT3 showed a corresponding statistically significant decrease (from  $4.1\pm 0.4$  to  $4.0\pm 0.4$  pmol/L [ $2.67\pm 0.26$  to  $2.60\pm 0.26$  pg/mL],  $p<0.001$ ). As a result, there was a statistically significant reduction in fT3/fT4 ratio ( $p<0.001$ ). Nonetheless, the changes of fT4, fT3 and fT3/fT4 ratio were not clinically significant as the absolute magnitude of change was small. There were only 3 (1.4%) abnormal TFTs post-vaccination. Two occurred among BNT162b2 recipients: both were subclinical thyrotoxicosis (TSH 0.32 mIU/L [ $0.32$  uIU/mL], fT4 11.51 pmol/L [ $0.89$  ng/dL] and fT3 4.40 pmol/L [ $2.86$  pg/mL]; TSH 0.34 mIU/L [ $0.34$  uIU/mL], fT4 12.67 pmol/L [ $0.98$  ng/dL] and fT3 4.22 pmol/L [ $2.74$  pg/mL]; both were anti-TPO and anti-Tg negative before and after vaccination). One occurred among CoronaVac recipients: isolated mild low fT3 (TSH 0.90 mIU/L [ $0.90$  uIU/mL], fT4 9.94 pmol/L [ $0.77$  ng/dL] and fT3 2.33 pmol/L [ $1.52$  pg/mL]; negative for anti-TPO and anti-Tg before and after vaccination). All three recipients were asymptomatic.

#### Changes in TFT and anti-thyroid antibody titres according to types of vaccines

While both vaccines were associated with a statistically significant reduction in fT3 (BNT162b2:  $p<0.001$ ; CoronaVac:  $p=0.036$ ) and fT3/fT4 ratio (both  $p<0.001$ ), we observed a statistically significant increase in TSH ( $p=0.001$ ) and fT4 ( $p<0.001$ ) only among CoronaVac recipients. Nonetheless, the absolute magnitude of change in TFTs was small.

Both anti-TPO and anti-Tg titres increased after either BNT162b2 or CoronaVac, although the change in anti-TPO after CoronaVac just failed to reach statistical significance ( $p=0.070$ ). The change in anti-Tg was comparable between the two types of vaccines, but the change in anti-TPO was greater among BNT162b2 recipients (BNT162b2: 3.10 IU/mL [IQR: 1.10 – 4.50] vs CoronaVac: 1.15 IU/mL [IQR: -1.50 – 3.68],  $p<0.001$ ).

#### Impact of pre-existing thyroid autoimmunity and changes in TFTs post-vaccination

Changes in TSH, fT4 and fT3 levels post-vaccination were comparable between individuals with and without pre-existing thyroid autoimmunity (**Table 4**).

#### Influence of age and sex on changes in TFTs and anti-thyroid antibody titres

Age did not correlate with the changes in TFTs or anti-thyroid antibody titres: TSH ( $p=0.559$ ), fT4 ( $p=0.837$ ), fT3 ( $p=0.692$ ), fT3/fT4 ratio ( $p=0.915$ ), anti-TPO ( $p=0.161$ ) and anti-Tg ( $p=0.978$ ).

Apart from the greater fT3 reduction in women than men (men:  $-0.03\pm 0.32$  pmol/L [ $-0.02\pm 0.21$  pg/mL] vs women:  $-0.13\pm 0.35$  pmol/L [ $-0.08\pm 0.23$  pg/mL];  $p=0.030$ ), there was no difference in changes in TSH ( $p=0.162$ ), fT4 ( $p=0.597$ ), fT3/fT4 ratio ( $p=0.092$ ), anti-TPO ( $p=0.144$ ) and anti-Tg ( $p=0.125$ ) between men and women.

#### Relationship between anti-thyroid antibody titres and NAb response

NAb responses were evaluated among 168 individuals at 8 weeks post-vaccination (121 [72.0%] received BNT162b2; 47 [28.0%] received CoronaVac). Among them, 11.6% of BNT162b2 recipients and 14.9% of CoronaVac recipients had evidence of pre-existing thyroid autoimmunity ( $p=0.559$ ).

NAb responses did not differ between those with and without pre-existing thyroid autoimmunity ( $p=0.855$ ) (Table 5). Furthermore, NAb titres post-vaccination did not correlate with baseline anti-TPO ( $p=0.880$ ) or anti-Tg ( $p=0.628$ ) titres. Similarly, NAb titres post-vaccination did not correlate with changes in anti-TPO ( $p=0.251$ ) or anti-Tg ( $p=0.702$ ) titres.

## Discussion

This is the first prospective evaluation of changes in anti-thyroid antibodies and thyroid function following different types of COVID-19 vaccination (BNT162b2 and CoronaVac). Our study showed that there was no overt thyroid dysfunction 8 weeks after either type of COVID-19 vaccination, although there was mild reduction in fT3/fT4 ratio, related to mild fT3 reduction and mild fT4 increase. Both anti-TPO and anti-Tg titres showed modest increase post-vaccination. Anti-TPO increase was greater among BNT162b2 recipients than CoronaVac recipients while anti-Tg increase was comparable between two groups. Incident anti-TPO positivity was rare and there was no incident anti-Tg positivity. Furthermore, pre-existing thyroid autoimmunity did not impair NAb responses following vaccination. Our results provided important reassurance to people to proceed to COVID-19 vaccination.

To date, more than 80 cases of thyroid dysfunction following COVID-19 vaccination have been reported in the literature. (7) As of 26 March 2022, more than 11 billion doses of COVID-19 vaccine have been given. The contrast between the number of the vaccine doses and the number of reports of thyroid dysfunction could be due to under-reporting or the truly rare incidence of post-vaccination thyroid dysfunction. Our study showed that there was no overt thyroid dysfunction, in keeping with a truly rare incidence of thyroid dysfunction following COVID-19 vaccination. From the literature, the onset time of thyroid dysfunction was usually around 2 weeks after each dose of

vaccination. (7) Hence, our 8-week study period was able to adequately cover this risk period. Notably, in addition to the commonly reported subacute thyroiditis and Graves' disease, there were a few reports of painless thyroiditis. (16,17) Painless thyroiditis can be under-reported because of less typical symptoms. Our study systematically assessed TFTs before and after vaccination, and did not reveal any case of painless thyroiditis. These were consistent with a recent study in Greece, in which Paschou *et al* systematically evaluated the impact of mRNA COVID-19 vaccination on TFTs and anti-thyroid antibody titres among 72 healthy subjects without known thyroid disorders, showing no incident overt thyroid dysfunction. (18)

Interestingly, among the cases of thyroid dysfunction after COVID-19 vaccination, there was only one report of a 61-year-old woman presenting with overt hypothyroidism 21 days after the second dose of Pfizer mRNA COVID-19 vaccine (19). The anti-TPO and anti-Tg titres were very high at presentation. She did not have any known thyroid or autoimmune disorders, but she had not received any prior TFT and anti-thyroid antibody measurements. Hence, it could not be determined whether this case represented previously undiagnosed hypothyroidism, worsening in hypothyroidism following COVID-19 vaccination, or incident Hashimoto's thyroiditis after COVID-19 vaccination. From the available evidence in cohort studies, Paschou *et al* (18) did not observe significant change in anti-thyroid antibody titres, or overt hypothyroidism after vaccination among 72 healthy individuals. Similarly, our study of over 200 individuals did not reveal incident overt hypothyroidism. Although we observed two recipients developing incident anti-TPO positivity, their anti-TPO titres were only mildly elevated. Taken together, the findings of these two cohort studies were not supportive of an association between COVID-19 vaccination and incident Hashimoto's thyroiditis or overt hypothyroidism.

Looking into the individual components of TFTs, we revealed a mild reduction in ft3/ft4 ratio following COVID-19 vaccination, driven by a combination of mild ft3 reduction and mild ft4 increase, but no statistically significant change in TSH. In the study done in Greece focusing on mRNA vaccine recipients, (18) Paschou *et al* reported a reduction in total T3 to a similar extent (0.07 nmol/L reduction; reference range of total T3: 0.84–2.6 nmol/L), no change in total T4, and a decrease in mean TSH from 2.06 mIU/L on day 1 to 1.84 mIU/L one month after the second dose of mRNA vaccine ( $p=0.037$ ). The changes in T3 and T4 were in line with our findings, when considering the BNT162b2 recipients in our study. However, we did not observe any changes in TSH among BNT162b2 recipients. The differences in baseline TSH might explain the difference in results obtained in these two studies: three individuals in the Greek study had elevated TSH (4.0–5.0 mIU/L), whereas all our subjects had normal TSH; mean TSH was 2.06 mIU/L in the Greek study, while median TSH was 1.10 mIU/L in our study. The T3 reduction post-vaccination, consistently observed by us and Paschou *et al*, is postulated to be analogous to the occurrence of non-thyroidal illness syndrome (NTIS), an adaptive response of the body to illness. Indeed, this has been well-recognized among COVID-19 patients of various severity. (20,21) Extrapolating from observations among COVID-19 survivors, the ft3 reduction is expected to recover within a few months. (21,22)

Our study extended the current understanding of TFTs post-vaccination by evaluating recipients of different COVID-19 vaccines. We showed that the post-vaccination reduction in ft3 and ft3/ft4 ratio was consistently seen among BNT162b2 and CoronaVac recipients, suggesting a phenomenon likely seen among all COVID-19 vaccine recipients. In contrast, we observed statistically significant differences in changes in TFTs between the two groups of vaccine recipients. There was an increase in ft4 post-CoronaVac reaching statistical significance, although the absolute magnitude of increase was small (0.38 pmol/L [0.03 ng/dL]). Among BNT162b2 recipients, ft4 showed a numerical increase but not reaching statistical significance. This could also be explained by the changes in thyroid

hormone metabolism in NTIS, where there could be a transient rise in T4 which coincide with the fall in T3. (23) Of note, as we reassessed all individuals at 8 weeks after baseline, reassessment TFTs were done at 4 weeks after the second dose of CoronaVac, but 5 weeks after the second dose of BNT162b2. Hence, it is possible that the reassessment TFTs for CoronaVac recipients captured the transient elevation in fT4, which was not seen among BNT162b2 recipients because the reassessment TFTs were measured after a relatively longer interval from the second dose. The significance of the modest rise in TSH (median change of 0.1 mIU/L [0.1 uIU/mL]) seen only among CoronaVac recipients remained to be elucidated with further follow-up. Nonetheless, no vaccine recipients developed subclinical hypothyroidism due to the modest rise in TSH.

Paschou *et al* measured the anti-thyroid antibody titres, but only reported qualitatively: no change in anti-TPO and anti-Tg antibody positivity before and after mRNA vaccination. (18) Our results were consistent with the above observation in that there was no significant change in anti-TPO and anti-Tg positivity post-vaccination. In the quantitative comparison, we further showed a modest increase in both anti-TPO and anti-Tg titres after BNT162b2 and CoronaVac. While the rise in anti-Tg titres were comparable between recipients of different vaccines, the anti-TPO rise was greater among BNT162b2 recipients. As mRNA vaccines, encoding the SARS-CoV-2 spike protein, intrinsically could engage innate immunity that instructs induction of immune protection, the higher reactogenicity of the mRNA vaccine may cause a dysregulated immune system leading to a greater increase in anti-TPO titres. (24,25) Despite the greater increase in anti-TPO titres, the absolute difference in titres was rather small and incident anti-TPO positivity was not observed among BNT162b2 recipients. Furthermore, the increase in anti-thyroid antibodies was not accompanied by incident thyroid dysfunction in the 8-week follow-up period. We believe that the small absolute increase in anti-thyroid antibody titres would unlikely lead to subsequent significant thyroid dysfunction. Nonetheless, this could only be ascertained by a longer-term surveillance of these vaccine recipients.

Data on NAb responses to COVID-19 vaccination among individuals with pre-existing thyroid autoimmunity are limited. Paschou *et al* (18) reported no difference in NAb responses to mRNA COVID-19 vaccination between patients with Hashimoto's thyroiditis and healthy controls. We took a step further to evaluate individuals with evidence of pre-existing thyroid autoimmunity but no thyroid dysfunction, showing similar NAb responses to COVID-19 vaccination compared with those without evidence of pre-existing thyroid autoimmunity. Together with our recent population-based analysis of safety of COVID-19 vaccination among patients treated for hypothyroidism (which include patients with Hashimoto's thyroiditis), (26) these results support the evidence-based recommendations that patients with thyroid autoimmunity should receive COVID-19 vaccination in the same way as for the general population. (14) Nonetheless, a recent case report described a 21-year-old woman with autoimmunity (Hashimoto's thyroiditis, pernicious anaemia and atrophic gastritis) who developed breakthrough Omicron infection 10 months after the second dose of mRNA vaccine in March 2021, despite previous infection by SARS-CoV-2 in November 2020 followed by two doses of mRNA vaccines (27). This case illustrates that patients with autoimmunity, even without immunosuppressants, may require careful monitoring with regard to the antibody response and decay following infection and vaccination.

Our study has certain limitations. Firstly, the follow-up duration was relatively short, up to 8 weeks post-vaccination. The follow-up duration was set based on the known onset time of thyroid dysfunction following COVID-19 vaccination reported in the literature. (7) TFTs and anti-thyroid antibodies were assessed only at baseline and 8-week post-vaccination. Hence, we could not exclude the possible occurrence of more significant TFT abnormalities before or after the 8-week assessment point. Secondly, the proportion of individuals with positive anti-TPO or anti-Tg at baseline was relatively small (only seen in 12.1%) for the evaluation of the influence of pre-existing thyroid



autoimmunity on NAb responses. As the anti-thyroid antibody titres were not high enough at baseline, our study could not adequately assess whether individuals having pre-existing autoimmunity or higher baseline anti-TPO or anti-Tg would develop overt hypothyroidism. We were also unable to determine the risk of exacerbation of Hashimoto's thyroiditis in patients with pre-existing disease as the number of participants with pre-existing disease was low. Thirdly, antibodies related to Graves' disease (anti-TSH receptor antibodies) were not tested in this study. Last but not least, as only mRNA and inactivated virus vaccines are provided by the Hong Kong SAR Government, our results may not be generalized to recipients of other types of COVID-19 vaccines such as the adenovirus-vectored vaccines.

## **Conclusion**

COVID-19 vaccination was associated with a modest increase in anti-thyroid antibodies, but did not lead to clinically significant thyroid dysfunction 8 weeks post-vaccination. NAb responses were not influenced by the presence of pre-existing thyroid autoimmunity. Our results provided important reassurance to people to proceed to COVID-19 vaccination.

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**Table 1.** Evolution of thyroid function and antibody titres of the seven individuals with abnormal baseline thyroid function tests

Patient	Age	Sex	Baseline					Vac	Reassessment at 8 weeks					Remarks
			TSH	ft4	ft3	Anti-TPO	Anti-Tg		TSH	ft4	ft3	Anti-TPO	Anti-Tg	
1	46	M	<b>0.04</b> mIU/L ( <b>0.04</b> uIU/mL)	13.60 pmol/L (1.06 ng/dL)	4.96 pmol/L (3.23 pg/mL)	7.3	16.1	BNT	<b>0.06</b> mIU/L ( <b>0.06</b> uIU/mL)	12.95 pmol/L (1.01 ng/dL)	4.38 pmol/L (2.85 pg/mL)	10.8	17.6	Persistent subclinical hyperthyroidism at 6-month follow-up
2	31	F	<b>0.14</b> mIU/L ( <b>0.14</b> uIU/mL)	11.46 pmol/L (0.89 ng/dL)	3.76 pmol/L (2.45 pg/mL)	6.4	15.5	BNT	0.80 mIU/L (0.80 uIU/mL)	9.88 pmol/L (0.77 ng/dL)	3.86 pmol/L (2.51 pg/mL)	7.9	19.6	
3	62	F	<b>0.19</b> mIU/L ( <b>0.19</b> uIU/mL)	10.11 pmol/L (0.79 ng/dL)	5.33 pmol/L (3.47 pg/mL)	18.8	16.3	Cor	<b>0.07</b> mIU/L ( <b>0.07</b> uIU/mL)	11.60 pmol/L (0.90 ng/dL)	4.74 pmol/L (3.09 pg/mL)	20.7	15.9	Normal TFT at 6-month follow-up
4	54	F	<b>0.28</b> mIU/L ( <b>0.28</b> uIU/mL)	11.21 pmol/L (0.87 ng/dL)	3.61 pmol/L (2.35 pg/mL)	<b>34.8</b>	10.5	BNT	<b>0.17</b> mIU/L ( <b>0.17</b> uIU/mL)	11.69 pmol/L (0.91 ng/dL)	4.31 pmol/L (2.81 pg/mL)	<b>42.9</b>	17.4	Normal TFT at 6-month follow-up
5	58	M	<b>0.30</b> mIU/L ( <b>0.30</b> uIU/mL)	11.10 pmol/L (0.86 ng/dL)	4.31 pmol/L (2.81 pg/mL)	7.1	10.6	Cor	0.45 mIU/L (0.45 uIU/mL)	11.81 pmol/L (0.92 ng/dL)	4.17 pmol/L (2.71 pg/mL)	12.9	14.4	
6	57	M	<b>0.34</b> mIU/L ( <b>0.34</b> uIU/mL)	13.23 pmol/L (1.03 ng/dL)	4.37 pmol/L (2.84 pg/mL)	7.9	12	Cor	0.58 mIU/L (0.58 uIU/mL)	12.77 pmol/L (0.99 ng/dL)	4.05 pmol/L (2.64 pg/mL)	7.8	16.7	
7	56	F	1.18	12.13	<b>6.28</b>	5.8	17.9	BNT	1.23	10.95	4.67	5.2	21.1	

			mIU/L (1.18 uIU/mL)	pmol/L (0.94 ng/dL)	pmol/L <b>(4.09)</b> pg/mL)				mIU/L (1.23 uIU/mL)	pmol/L (0.85 ng/dL)	pmol/L (3.04 pg/mL)			
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Abbreviations: M, male; F, female; TSH, thyroid-stimulating hormone; ft4, free thyroxine; ft3, free triiodothyronine; anti-TPO, anti-thyroid peroxidase; anti-Tg, anti-thyroglobulin; TFT, thyroid function test; Vac, vaccine; BNT, BNT162b2; Cor, CoronaVac

Units: age (years); anti-TPO (IU/mL), anti-Tg (IU/mL)

Values outside the reference ranges are in bold



**Table 2** Baseline characteristics of the cohort

Baseline variables	Vaccine			p-value
	All (n=215)	BNT162b2 (n=129)	CoronaVac (n=86)	
Age, year	49.6 ± 12.5	47.5 ± 12.4	52.8 ± 12.1	<b>0.002</b>
Men (%)	80 (37.2)	49 (38.0)	31 (36.0)	0.886
Obesity (%)	8 (3.7)	7 (5.4)	1 (1.2)	0.149
IHD (%)	11 (5.1)	5 (3.9)	6 (7.0)	0.354
Heart failure (%)	1 (0.5)	0 (0)	1 (1.1)	0.400
Stroke (%)	5 (2.3)	3 (2.3)	2 (2.3)	0.999
Cancer (%)	12 (5.6)	6 (4.7)	6 (7.0)	0.549
Diabetes (%)	17 (7.9)	8 (6.2)	9 (10.5)	0.381
Hypertension (%)	38 (17.7)	22 (17.1)	16 (18.6)	0.913
Hyperlipidaemia (%)	74 (34.4)	48 (37.2)	26 (30.2)	0.364
Chronic liver disease (%)	17 (7.9)	10 (7.8)	7 (8.1)	0.999
Asthma / COPD (%)	6 (2.8)	3 (2.3)	3 (3.5)	0.685

Baseline variables	Vaccine			p-value
	All (n=215)	BNT162b2 (n=129)	CoronaVac (n=86)	
TSH, mIU/L*	1.10 (0.85 – 1.50)	1.10 (0.86 – 1.47)	1.12 (0.83 – 1.52)	0.870
TSH, uIU/mL*	1.10 (0.85 – 1.50)	1.10 (0.86 – 1.47)	1.12 (0.83 – 1.52)	
Free T4, pmol/L	12.0 ± 1.11	11.9 ± 1.09	12.0 ± 1.16	0.775
Free T4, ng/dL	0.93 ± 0.09	0.92 ± 0.08	0.93 ± 0.09	
Free T3, pmol/L	4.12 ± 0.41	4.14 ± 0.40	4.09 ± 0.44	0.439
Free T3, pg/mL	2.68 ± 0.27	2.70 ± 0.26	2.66 ± 0.29	
CRP, mg/L*	1.00 (1.00 – 1.66)	1.00 (1.00 – 1.50)	1.00 (1.00 – 1.90)	0.225
Anti-Tg, IU/mL*	12.4 (11.1 – 14.9)	12.2 (11.0 – 14.9)	12.7 (11.3 – 14.8)	0.877
Positive Anti-Tg (%)	17 (7.9)	11 (8.5)	6 (7.0)	0.877
Anti-TPO, IU/mL*	7.50 (5.90 – 11.2)	6.90 (5.70 – 10.0)	8.60 (6.70 – 12.8)	0.480
Positive anti-TPO (%)	22 (10.2)	15 (11.6)	7 (8.1)	0.550
Positive anti-TPO/Tg (%)	26 (12.1)	16 (12.4)	10 (11.6)	0.999

Data are reported as mean ± SD or median (interquartile range). \*Log-transformed before analysis.

IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; TSH, thyroid stimulating hormone; TFT, thyroid function test; CRP, C-reactive protein; Tg, thyroglobulin; TPO, thyroid peroxidase

**Table 3** Thyroid function and anti-thyroid antibody titres before (pre) and after (post) COVID-19 vaccination

Variables	All (n = 215)		p-value	Vaccine					
				BNT162b2 (n = 129)		p-value	CoronaVac (n = 86)		p-value
	Pre	Post		Pre	Post		Pre	Post	
TSH, mIU/L*	1.10 (0.85 – 1.50)	1.17 (0.84 – 1.54)	0.225	1.10 (0.86 – 1.47)	1.09 (0.81 – 1.49)	0.401	1.12 (0.83 – 1.52)	1.27 (0.93 – 1.62)	<b>0.001</b>
TSH, uIU/mL*	1.10 (0.85 – 1.50)	1.17 (0.84 – 1.54)		1.10 (0.86 – 1.47)	1.09 (0.81 – 1.49)		1.12 (0.83 – 1.52)	1.27 (0.93 – 1.62)	
ΔTSH, mIU/L*				-0.03 (-0.3 – 0.21)			0.12 (-0.14 – 0.36)		<b>0.004</b>
ΔTSH, uIU/mL*				-0.03 (-0.3 – 0.21)			0.12 (-0.14 – 0.36)		
Free T4, pmol/L	12.0 ± 1.11	12.2 ± 1.20	<b>&lt;0.001</b>	11.9 ± 1.09	12.1 ± 1.07	0.131	12.0 ± 1.16	12.4 ± 1.34	<b>&lt;0.001</b>
Free T4, ng/dL	0.93 ± 0.09	0.95 ± 0.09		0.92 ± 0.08	0.94 ± 0.08		0.93 ± 0.09	0.96 ± 0.10	
ΔFree T4, pmol/L				0.10 ± 0.77			0.38 ± 0.90		<b>0.019</b>
ΔFree T4, ng/dL				0.01 ± 0.06			0.03 ± 0.07		
Free T3, pmol/L	4.12 ± 0.41	4.03 ± 0.42	<b>&lt;0.001</b>	4.14 ± 0.40	4.03 ± 0.42	<b>&lt;0.001</b>	4.09 ± 0.44	4.02 ± 0.42	<b>0.036</b>

Variables	All (n = 215)		p-value	Vaccine					
				BNT162b2 (n = 129)		p-value	CoronaVac (n = 86)		p-value
	Pre	Post		Pre	Post		Pre	Post	
Free T3, pg/mL	2.68 ± 0.27	2.62 ± 0.27		2.70 ± 0.26	2.62 ± 0.27		2.66 ± 0.29	2.62 ± 0.27	
ΔFree T3, pmol/L				-0.11 ± 0.35			-0.08 ± 0.34		0.567
ΔFree T3, pg/mL				-0.07 ± 0.23			-0.05 ± 0.22		
T3/T4 ratio	0.347±0.043	0.333±0.043	<b>&lt;0.001</b>	0.349±0.040	0.337±0.041	<b>&lt;0.001</b>	0.344±0.044	0.327±0.045	<b>&lt;0.001</b>
ΔT3/T4 ratio				-0.012±0.032			-0.016±0.034		0.356
CRP, mg/L*	1.00 (1.00 – 1.67)	1.00 (1.00 – 1.50)	0.315	1.00 (1.00 – 1.50)	1.00 (1.00 – 1.20)	0.292	1.00 (1.00 – 1.90)	1.00 (1.00 – 1.98)	0.702
CRP positivity (%)	11 (5.12)	13 (6.05)	0.754	5 (3.88)	7 (5.43)	0.625	6 (6.98)	6 (6.98)	0.999
Anti-Tg, IU/mL*	12.4 (11.1 – 14.9)	15.7 (14.2 – 18.2)	<b>&lt;0.001</b>	12.2 (11.0 – 14.9)	15.6 (14.2 – 18.2)	<b>&lt;0.001</b>	12.7 (11.3 – 14.8)	15.9 (14.4 – 17.9)	<b>&lt;0.001</b>

Variables	All (n = 215)		p-value	Vaccine					
				BNT162b2 (n = 129)		p-value	CoronaVac (n = 86)		p-value
	Pre	Post		Pre	Post		Pre	Post	
$\Delta$ Anti-Tg, IU/mL*				3.40 (1.90 – 4.50)			3.50 (1.60 – 4.60)		0.678
Positive anti-Tg (%)	17 (7.91)	15 (6.98)	0.500	11 (8.53)	9 (6.98)	0.500	6 (6.98)	6 (6.98)	0.999
Anti-TPO, IU/mL*	7.50 (5.90 – 11.2)	9.80 (7.80 – 13.1)	<b>&lt;0.001</b>	6.90 (5.70 – 10.0)	9.80 (8.50 – 13.4)	<b>&lt;0.001</b>	8.60 (6.70 – 12.8)	9.30 (7.10 – 12.5)	0.070
$\Delta$ Anti-TPO, IU/mL*				3.10 (1.10 – 4.50)			1.15 (-1.50 – 3.68)		<b>&lt;0.001</b>
Positive anti-TPO (%)	22 (10.2)	24 (11.2)	0.500	15 (11.6)	15 (11.6)	0.999	7 (8.14)	9 (10.5)	0.500
Positive anti-TPO/Tg (%)	26 (12.1)	27 (12.6)	0.500	16 (12.4)	15 (11.6)	0.999	10 (11.6)	12 (14.0)	0.500

Data are reported as mean  $\pm$  SD or median (interquartile range). \*Log-transformed before analysis.

Abbreviations: TSH, thyroid stimulating hormone; TFT, thyroid function test; CRP, C-reactive protein; Tg, thyroglobulin; TPO, thyroid peroxidase;  $\Delta$ , changes in the parameter (post – pre)

**Table 4.** Changes in thyroid function parameters according to baseline anti-thyroid antibody positivity

	Anti-TPO and anti-Tg negative (n = 189)	Anti-TPO or anti-Tg positive (n = 26)	p-value
Change in TSH (mIU/L)*	0.04 (-0.21 – 0.29)	0.05 (-0.28 – 0.28)	0.394
Change in TSH (uIU/mL)*	0.04 (-0.21 – 0.29)	0.04 (-0.21 – 0.29)	
Change in free T4 (pmol/L)	0.22 ± 0.85	0.19 ± 0.71	0.872
Change in free T4 (ng/dL)	0.02 ± 0.07	0.01 ± 0.06	
Change in free T3 (pmol/L)	-0.10 ± 0.34	-0.07 ± 0.39	0.640
Change in free T3 (pg/mL)	-0.07 ± 0.22	-0.05 ± 0.25	

\* logarithmically transformed before analyses

Change of the parameters = post – pre

Abbreviations: TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine; TPO, thyroid peroxidase; Tg, thyroglobulin

**Table 5.** Neutralizing antibody responses according to baseline thyroid autoimmunity (n=168)

<b>Neutralizing antibody response</b>	<b>Anti-TPO and anti-Tg negative (n=147)</b>	<b>Anti-TPO or anti-Tg positive (n=21)</b>
Negative	8 (5.4%)	1 (4.8%)
Indeterminate	4 (2.7%)	1 (4.8%)
Positive	135 (91.8%)	19 (90.5%)

Abbreviations: anti-TPO, anti-thyroid peroxidase; anti-Tg, anti-thyroglobulin

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