Subacute thyroiditis after SARS-CoV2 vaccines – a systematic review

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Subacute thyroiditis after SARS-CoV2 vaccines – a systematic review

During the pandemic of Coronavirus disease, many procedures and restrictions were implemented to stop the spread of the virus, though none of which is as efficient as vaccination. COVID-19 vaccines are vital for returning to a time before the pandemic. Moreover, analyzing the protective effects and complications of vaccines it is crucial to minimize its adverse effects. Our review analyzed 28 cases described in medical journals, of patients who developed subacute thyroiditis (SAT) after COVID-19 vaccines. Most commonly, SAT follows upper respiratory tract infections. Until 2016 only 5 cases of SAT after vaccinations had been reported. After COVID-19 vaccines, SAT developed mostly among women. Most cases were observed after the first dose, after seven days on average. In all presented patients, symptoms were similar, including mostly hyperthyroidism signs and pain. TSH level among 81% was low or undetectable. Treatment in most cases included anti-inflammatory and analgesic medications, propranolol hydrochloridum, and glucocorticoids, leading to full recovery. SAT occurs in healthy individuals with negative infection and thyroid disease medical history as well as in patients associated with thyroid diseases. The mechanism, which may lead to subacute thyroiditis, may be complex and involves angiotensin-converting enzyme 2 (ACE2) receptors, cross-reactions between thyroid peroxidase and spike protein, and the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Cross-reaction between thyroid peroxidase and spike protein, nucleoproteins, and membrane protein of SARS-CoV-2 was proved on animal models. SARS-CoV2 infection mechanism requires the presence of ACE2 receptors and transmembrane serine protease (TMPRSS2), which were both found in thyroid follicular cells. Spike protein produced after vaccination, is modified (HexaPro), and it is more stable and binds higher than native viral protein. Some authors suggest that in effect it may lead to pyroptosis and thyroid cells destruction. Another potential mechanism of post-vaccine SAT is ASIA, which manifests with various symptoms, and although it is undermined by many health professionals some authors diagnosed ASIA in patients with SAT. SAT is a self-limiting disease and non-life-threatening. However, the diagnosis is very important, especially in individuals with risk factors of cardiovascular disease to prevent side effects of hyperthyroidism like cardiac arrhythmias, tachycardia, coronary syndromes, and side effects from other organs.

Keywords: thyroid gland, thyroiditis, subacute, COVID-19, vaccine.

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Introduction

On 11th March, The World Health Organization (WHO) announced the pandemic of Coronavirus disease (COVID-19). The pandemic has resulted in many deaths, health complications, and economic crisis. Countless procedures and restrictions were implemented to stop the spread of the virus. Till that moment, 5.36 million people died from COVID-19. Vaccination is the key to decreasing mortality and morbidity and it is crucial to stop the health and economic crisis[1]. Vaccines against COVID-19 are highly effective and safe according to conducted studies. Adverse drug reactions are tolerated and the benefits of vaccination outweigh the risks. However, as in other medical novelties, we experience new complications that can be easily solved.

Materials and Methods

We conducted a systematic review of studies from PubMed published between December 2020 and November 2021, NCBI, Google Scholar which reported on patients who suffered subacute thyroiditis (de Quervain thyroiditis, SAT) after the COVID-19 vaccine. We used the phrases “thyroiditis COVID-19 vaccine”, “SAT COVID-19 vaccine”, “thyroid COVID-19” to search PubMed. We found 552 publications and we used 19 studies: every case report and case series. We rejected articles not referring to particular patients or described problems displayed by mentioned databases. Included 27 patients who had symptoms and/or laboratory tests relevant to subacute thyroiditis, which appeared up to a month after vaccination against COVID-19.

Literature Review

The first registered vaccine against COVID-19 was Gam-COVID-Vac (Sputnik V), which is a viral vector vaccine based on two recombinant replication-defective human adenoviruses (26 and 5) [2]. Vaccine effectiveness for preventing laboratory-confirmed infections is 78.6% and for reducing hospitalizations and deaths was 87.6% according to Soledad González et al.[3]

Tozinameran, the mRNA vaccine, code name: BNT162b2 by Pfizer and BioNTech called Comirnaty is a novel vaccine, which uses messenger RNA (mRNA) to induce an immunological response. mRNA encodes the spike protein of SARS-CoV-2 and once the mRNA enters the cells, the spike proteins are made to induce an immunological response. The effectiveness of the vaccine by Pfizer and BioNTech is

about 95% in the prevention of severe COVID-19 infection[4].

mRNA1273, developed by Moderna, also an mRNA vaccine, is a 2-dose vaccine, administered in the interval of 28 days. Its efficiency is 94.1%. Similarly to Tozinameran consists of modified mRNA, encoding SARS-CoV-2-spike protein, located inside lipid nanoparticles.

The Oxford–AstraZeneca COVID-19 vaccine (ChAdOx1 nCoV-19) code name: AZD1222 by AstraZeneca, brand names Vaxzevria and Covishield consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 spike protein antigen gene[5]. The Efficiency of the 2-dose AstraZeneca vaccine is 70.4% and this is the most commonly used vaccine worldwide against COVID-19. There were some reports about an increased rate of thrombotic thrombocytopenia after the ChAdOx1 nCoV-19 vaccine, which clinically mimics autoimmune heparin-induced thrombocytopenia. However, these kinds of complications are very rare and the benefits of the vaccine outweigh the risks [7].

Janssen COVID-19 vaccine, code name Ad26.COV2.S is the vaccine, which consists of replication-deficient adenovirus type 26 and contains a full-length SARS-CoV-2 S protein. Efficacy of Ad26.COV2.S against severe COVID-19 infection was 66.9% [8].

We collected vaccines permitted by the World Health Organization in the table, also with the vaccines not mentioned above (table 1).

There are three types of subacute thyroiditis based on a clinical presentation: acute, subacute, and chronic. The histological classification includes bacterial and non-bacterial thyroiditis such as chronic lymphocytic thyroiditis called Hashimoto disease, subacute lymphocytic thyroiditis, or subacute granulomatous thyroiditis known as subacute thyroiditis (SAT).

Subacute thyroiditis usually happens after viral upper respiratory tract infection and also after SARS-CoV-2 infection. Initially, symptoms include painful swelling of the thyroid gland and a fever. The pain usually radiates to the mandibular angle, ear, and upper chest but the painless clinical presentation was also observed, including COVID-19 patients. Thyrotoxicosis, occurring during the first phase of the disease, usually does not present any features, however fatigue and muscle pain can be noticed. The hypothyroidism phase does not always occur. The treatment of subacute thyroiditis lasts few weeks. During the hyperthyroidism phase, there is no requirement to use antithyroid treatment, although propranolol hydrochloridum may be considered. The treatment consists of anti-inflammatory and analgesic

Tabela 1. Szczepienia na SARS-CoV-2, zaaprobowane przez WHO [Stan na 10.12.2021].

Table 1. WHO-approved SARS-CoV-2 vaccines. [Last update 10.12.2021].

Vaccine name	Manufacturer	Type	Doses	Interval	Most common adverse reactions
Comirnaty Tozinameran (BNT162b2)	Pfizer and BioNTech	mRNA-based	2	3 weeks	pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain [9]
Spikevax (mRNA1273)	Moderna	mRNA-based	2	4 weeks	pain, redness or swelling at the site of vaccine shot, fever, fatigue, headache, muscle pain, nausea, vomiting, itching, chills, and joint pain [9]
Vaxzevria (AZD1222) (ChAdOx1 nCoV-19 vaccine)	ASTRA ZENECA	viral vector	2	4–12 weeks	tenderness or pain of arm due to injection, headache, fatigue, chills and fever, diarrhoea [6]
Covishield (AZD1222) (ChAdOx1 nCoV-19 vaccine)	Serum Institute of India	viral vector	2	4–12 weeks	as Vaxzevria.
Janssen COVID-19 vaccine (Ad26.COV2.S)	Johnson & Johnson	viral vector	1	–	pain at the inoculation site and systemic signs such as fever, headache, myalgia, or nausea [8]
COVIL (BBIBP-CorV) (Vero Cells)	Sinopharm	inactivated virus	2	3–4 weeks	injection site pain, fatigue, and headache, lethargy, tenderness [10]
CoronaVac	Sinovac Biotech	inactivated virus	2	4 weeks	localized pain at the injection site, Fatigue, muscle pain, and headache [11]
Covaxin (BBV152)	Bharat Biotech	inactivated virus	2	4 weeks	pain and swelling at the injection site, and systemic adverse events were fever, fatigue or malaise, myalgia, body aches, headache, nausea or vomiting, anorexia, chills, generalised rash, and diarrhoea. [12]

medications such as acidum acetylsalicylicum or non-steroidal anti-inflammatory drugs (NSAIDs). In the case of lack of effect and continuing pain, glucocorticoids (GCs) could be included in the treatment. In the hypothyroid phase, Levothyroxine (LT4), which is preventing deterioration, should be considered. Subacute thyroiditis is a self-limiting illness and it does not permanently damage the thyroid.

Although SAT is connected with viral upper respiratory tract infections, subacute thyroiditis can be rarely observed after vaccinations. Till 2016 there were only five published reports of SAT after the viral vaccine [13, 14]. Since then, new reports were available but still, we are dealing with extremely rare adverse effects. In the era of research on the COVID-19 vaccine the growing number of reports on SAT after vaccine appear.

Results

There were 19 studies, which described 27 patients with thyroiditis after the COVID-19 vaccine. We present the table with a summary of available cases (table 2). Majority of the patients who suffered SAT after the COVID-19 vaccine were women, which coincides with the epidemiology of SAT. 55.5% of patients (15 patients) had SAT after the first dose of the vaccine and 37% (10 patients) of patients after the second one. After the second dose symptoms were being observed earlier (average 7.25 vs. 9.33 days). 81% of patients had low or even undetectable thyroid-stimulating hormone (TSH) level and no one had elevated TSH level. In

this patient population, SAT occurred mainly after mRNA vaccination (48%).

Patients suffered similar symptoms which were: neck pain (23 out of 27 patients), fever (8 patients), and signs of thyrotoxicosis: heart palpitations (10 patients), fatigue (6 patients), weight loss (6 patients), or insomnia (1 patient). Patients were treated with NSAIDs or other analgesics (12 patients), propranololi hydrochloridum (10 patients), and with GCs (15 patients).

Potential mechanisms

COVID-19 infection causes direct thyroid cytotoxic reactions and glands dysfunction. [35, 36]. Angiotensin-converting enzyme 2 (ACE2) is a transmembrane metalloproteinase, physiologically a regulator of the renin-angiotensin-aldosterone system (RAAS), its main function is angiotensin conversion to its active form. Whole RAAS controls the blood pressure and vasoconstriction, and also homeostasis of body fluids, inflammation, and fibrosis. Coronaviruses utilize ACE2 to infect cells as a receptor for host cell entry. ACE2 consists of an N-terminal peptidase domain (PD) and a C-terminal collectrin-like domain (CLD) [37, 38].

Transmembrane serine protease 2 (TMPRSS2), a known human airway and alveolar protease must interact with ACE2 in cellular exocytic pathways for membrane fusion to occur. TMPRSS2 cleavages SARS-CoV-2 spike protein (SARS-2-S) and enables it to bind with ACE2 [39–41]. During both infection and vaccination, SARS-2-S is cleaved into two subunits: S1 and S2. S1 subunit interacts with

Tabela 2. Pacjenci ze zdiagnozowanym podoстрыm zapaleniem tarczycy (SAT) po szczepieniu przeciwko COVID-19.

Table 2. Patients with subacute thyroiditis (SAT) after COVID vaccine.

Age, sex	Vaccine	Time after vaccination	Diagnosis	Symptoms	Examination	TSH, T3, T4	Treatment
46 yo F, * [15]	Moderna	Several d.	SAT	right-sided neck pain, fever, myalgia	tender, swollen and warmer area of the anterior neck with firm nodule-like structure and normal overlaying skin, hypertension, tachycardia	TSH – undetectable T3, T4 – elevated	analgesics, GCs, propranololi hydrochloridum
42 yo F, * [16]	Pfizer/BioNTech	5 d. after 1 st dose	SAT	sore throat, palpitations	tachycardia with sinus tachycardia on ECG	TSH low fT4, fT3 – elevated	NSAIDs, GCs, propranololi hydrochloridum
26 yo, F, * [17]	AstraZeneca	2 d. after 1 st dose	SAT	cervical pain radiating to ears, fever, chills, tenderness in the thyroid region with pain on palpation, cervical lymphadenopathy	tenderness in the thyroid area, painful during palpation	TSH – normal T3 – elevated T4 – normal	NSAIDs, GCs
49 yo, F, * [17]	Moderna	1 month after 1 st dose	SAT	sore throat with radiation to the ear, headaches and difficulty in concentrating, pain on palpation of a cervical area	pain on palpation of a cervical area	TSH, T3, T4 – normal	NSAIDs, GCs
55 yo, F, * [18]	AstraZeneca	3 w. after 1 st dose	SAT	neck pain and swelling, headache, sore throat, generalized aches and palpitations	tender goiter	TSH – low fT4 – elevated	NSAIDs, acetaminophen, propranololi hydrochloridum
67 yo, M [19]	Vero Cell	No information, after 2 nd dose	SAT	pain in the anterior neck and the left ear,	minimal tenderness in the thyroid palpation, atrial extra beats	TSH – low fT3, fT4 – elevated	NSAIDs
38 yo, F, * [20]	CoronaVac	2 w. after 2 nd dose	SAT	swelling in the neck, pain, fatigue, loss of appetite and sweating in the evening	goiter with pain in the right thyroid lobe during palpation	TSH – low fT3, fT4 – elevated	NSAIDs, propranololi hydrochloridum
34 yo, F [21]	Covaxin	5–7 d. after 1 st dose	SAT	fatigue, myalgia, mild fever, palpitation, and radiating anterior neck pain	tenderness of thyroid gland and its enlargement	TSH – low fT3, fT4 – elevated	GCs, propranololi hydrochloridum
47 yo, F, * [22]	AstraZeneca	2 w. after 1 st dose	SAT	fever and neck pain radiating to the jaw, restlessness difficulty in swallowing and weight loss	tachycardia, tender goiter	TSH – low fT3, fT4 – elevated	propranololi hydrochloridum
39 yo, F, * [23]	AstraZeneca	4 d. after 2 nd dose	SAT	neck pain	-----	TSH – low fT4 – elevated	no information
73yo, F [23]	AstraZeneca	11 d. after 2 nd dose	SAT	fever, neck pain	-----	TSH – low fT4 – elevated	no information
50 yo, F [24]	AstraZeneca	10 d. after 1 st dose	SAT	neck pain, sore throat, dyspnoea, palpitations, tremor	sinus tachycardia, tenderness of thyroid gland	TSH – low fT4 – elevated	carbimazole
42 yo, F [25]	Moderna	5–6 d. after 1 st dose	SAT	bilateral ear pain radiating down to the lateral and anterior neck and bilateral lower jaw, elevating during turning head, swallowing and coughing	anterior neck swelling with tenderness on palpation	TSH – low fT3 – low fT4 – normal	NSAIDs
48 yo, M [26]	No information	1 w. after the 2 nd dose	SAT	right neck swelling, throat discomfort, palpitations	tenderness and swelling in the thyroid gland area	TSH – low fT4 – elevated	NSAIDs, GCs
35 yo, F [27]	CoronaVac®	4 d. after the 2 nd dose	SAT	neck pain radiating to the right side, palpitation, fever, fatigue	enlargement, sensitivity and tenderness on palpation of thyroid gland	TSH – normal fT3 – elevated fT4 – normal	GCs, propranololi hydrochloridum

Tabela 2. Pacjenci ze zdiagnozowanym podostrym zapaleniem tarczycy (SAT) po szczepieniu przeciwko COVID-19 (cd.).

Table 2. Patients with subacute thyroiditis (SAT) after COVID vaccine (cont.).

Age, sex	Vaccine	Time after vaccination	Diagnosis	Symptoms	Examination	TSH, T3, T4	Treatment
34 yo, F [27]	CoronaVac®	4 d. after the 1 st dose	SAT	neck pain, fatigue, and weight loss, fever, palpitation	bilateral sensitivity of the thyroid gland on palpation	TSH – low fT3 – elevated fT4 – normal	GCs, propranololi hydrochloridum
37 yo, F [27]	CoronaVac®	7 d. after the 2 nd dose	SAT	neck pain	tenderness on palpation over the right lobe of the thyroid gland	TSH – normal fT3 – elevated fT4 – normal	no treatment
Middle age, F [28]	Pfizer/BioNTech	2 w. after 2 nd dose	SAT	painful swelling of the thyroid gland and symptoms of thyrotoxicosis, including poor sleep, worsening night sweats, hyper defaecation and weight loss		TSH – low T3 – normal fT4 – elevated	NSAIDs
About 30 yo, F [29]	Pfizer/BioNTech	6 d. after 1 st dose	SAT	find in histopathological examination after lobectomy			-----
51 yo, F [30]	Pfizer–BioNTech	4 d. after 1 st dose	SAT	nausea, mild anterior neck pain and fever	tenderness of the thyroid gland on palpation	TSH – low fT4 – elevated	GCs
39 yo, F [30]	Astra Zeneca	3 w. after, no information about dose	SAT	no clinical symptoms	no findings	TSH – low TT3 – normal fT4 – elevated	-----
35 yo, F [31]	Pfizer/BioNTech	12 d. (after 1 st dose)	SAT	neck pain, fatigue, palpitations	tenderness on palpation of the thyroid region	TSH – low fT4 – elevated	GCs
32 yo F [31]	Pfizer/BioNTech	4 d. (after 2 nd dose)	SAT	neck pain, fatigue	tenderness on palpation of the thyroid region	TSH – low fT4 – normal	GCs
35 yo, F [32]	Pfizer/BioNTech	4 d. after 1 st	SAT	right sided neck pain	no information	TSH – low fT3, fT4 – elevated	no information
38 yo, F [33]	Moderna	8 d. after 1 st dose	SAT	anterior cervical pain, palpitations, distal tremor, axillar and inguinal bilateral ganglionic reaction	enlargement of the right thyroid lobe, painful on palpation	TSH – low fT3, fT4 – elevated	GCs, propranololi hydrochloridum and NSAIDs
32 yo, male [33]	Pfizer/BioNTech	10 days after 1 st dose	SAT	weight loss, nervousness and insomnia	no information	TSH – low fT4 – elevated 8 weeks later TSH – elevated fT4 – low	levothyroxine
40 yo, F [34]	Pfizer/BioNTech	12 hours after 2 nd dose	SAT	malaise and severe anterior neck pain 26 days after vaccination: bony aches, exhaustion, emotional lability, palpitations and hyperhidrosis	neck tenderness	TSH – low fT4 – elevated	GCs, propranololi hydrochloridum

yo – wiek w latach, F – kobieta, M – mężczyzna, d. – dni, w. – tygodnie, SAT – podostre zapalenie tarczycy, GCs – kortykosteroidy,

* – brak chorób w wywiadzie, NSAIDs – niesteroidowe leki przeciwzapalne.

yo – years old, F – female, M – male, d. – days, w. – weeks, SAT – subacute thyroiditis, GCs – glicocortyosteroids,

* – no past medical history, NSAIDs – Nonsteroidal anti-inflammatory drug.

ACE2 throughout its receptor-binding domain (RBD) connects with PD of ACE2. Whereas S2 acts as an anchor and is indispensable for membrane fusion to occur, essential for viral cell entry. SARS-2-S developing in mRNA vaccinated patients, called HexaPro, slightly differ from the original SARS-CoV-2-spike protein and that is the reason why is more stable and binds higher than native viral

protein [37, 42, 43]. Both ACE2 and TMPRSS2 are expressed on follicular thyroid cells and therefore the tissue is vulnerable to being stimulated by spike protein [44, 45]. Spike protein interacting with ACE2 causes excessive pyroptosis [46].

The autoimmune/inflammatory syndrome induced by adjuvants (ASIA) is a medical condition introduced by Shoenfeld et al. in 2011 [47].

The disease is the result of contact of the adjuvants present in vaccines with an organism. Adjuvants are required to generate immunological response after vaccine but genetically predisposed individuals may trigger ASIA. Clinical manifestation of ASIA may be heterogeneous despite proposed clinical criteria for diagnosis. Since detection of ASIA, about a few thousand cases of the disease were reported, the most after vaccines against human papillomavirus, hepatitis B, and influenza [27]. One of the major criteria of ASIA syndrome is exposure to external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations, which can possibly be fulfilled in patients after the COVID-19 vaccine [47]. Two cases of ASIA syndrome were described by Olga Vera-Lastra et al., wherein the patients were diagnosed with Graves-Basedow (GB) syndrome after vaccination as a trigger factor and fulfill the criteria of ASIA syndrome [48].

Furthermore, Aristo Vojdani et al. found in the animal model that SARS-CoV-2 antibodies have reactions with many tissues in human organisms, inter alia thyroid gland. SARS-CoV-2 spike protein, nucleoprotein, and membrane protein all cross-reacted with thyroid peroxidase, and many thyroid peroxidase peptide sequences were similar to sequences in various SARS-CoV-2 proteins [49]. Besides ASIA syndrome, it could also explain reported cases of GB disease after COVID-19 vaccination [48]. The autoimmune reaction of antibodies against spike protein could affect thyroid cells and constitute a trigger factor for autoimmune diseases as Graves-Basedow [27, 49]. It may be suspected that in the development of the GB disease participate more than one factor which may be connected with vaccination. Therefore, it cannot be excluded that this type of reaction could be the reason for subacute thyroiditis as the destruction of follicular cells is the first stage of the pathophysiology of SAT.

Discussion

The authors do not question the necessity of a wide scale of COVID-19 vaccination, helping to handle the pandemic, based on the current evidence, the benefits of the vaccines outweigh the risk of adverse effects [50]. To our knowledge, there is a lack of reviews about SAT after COVID-19 vaccinations. This is the first publication that gathers all cases available in the literature.

We trust that the fact about the rare but not insignificant complication which is SAT after COVID-19 vaccine will contribute to simplifying the diagnostics and therapeutic process in these patients. Further analysis is necessary to

determine if SAT is more frequent after the COVID-19 vaccine than other vaccines and to determine if there is a possibility to prevent it. SAT after the COVID-19 vaccination can be successfully treated and cannot lead to the omission of vaccination, however, that adverse effect should be taken under consideration. SAT complications, such as arrhythmias can be threatening, especially among patients with coexisting cardiovascular diseases, thus its diagnosis and treatment are crucial. The review of the literature shows that SATs occur after every vaccine type, thus further studies on the occurrence of this complication are required to answer what is the most suitable vaccine among patients with SAT and cardiovascular risk factors.

Many mechanisms are possibly involved in the pathophysiology of SAT after the COVID-19 vaccine, which we mentioned in this article. Molecular mechanisms may be much more complicated than we could conceive and may be connected with ACE2 receptors, ASIA syndrome, antibodies directed against thyroid tissue mimicking the virus SARS-CoV2 proteins.

As a potential mechanism of thyroiditis, we consider the effect of post-vaccine spike proteins on ACE2. It corroborates the occurrence of SAT after all types of vaccines, which common denominator is the synthesis of the spike protein. We suppose that post-vaccine spike proteins might interact with ACE2 present on thyroid cells, beginning excessive pyroptosis leading to thyroiditis. However, further molecular research is necessary to recognize differences between the spike protein of the virus and ones synthesized after vaccination.

The second mechanism that we and other authors take under consideration is an excessive inflammatory reaction to adjuvant substances present in COVID-19 vaccines, causing an autoimmune reaction of antibodies against spike proteins, triggering thyroiditis. Adjuvants differ though in all types of vaccines, therefore it is not possible to distinguish one substance responsible for ASIA syndrome.

Conclusion

SAT is an adverse reaction of vaccination of unspecified occurrence. COVID-19 vaccines are harmless, and their beneficial effects are overwhelming potential risks of adverse effects. The SARS-Cov-2 infection itself complicates with multiple diseases, including thyroid gland disorders [35]. Finally, SAT is a curable disease with accessible, widespread drugs, when diagnosed. However, it is of special meaning to keep in mind the possibility of SAT occurrence. Proper diagnosis of SAT

is crucial for undertaking an adequate treatment to prevent complications, such as thyrotoxicosis, cardiac arrhythmias, hypertension, deterioration of chronic heart failure. Our analysis has limitations. First of all, there is no clear molecular evidence and the cause-effect relationship between vaccination and SAT. Not every mentioned case report provided sufficiently precise information about patients.

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