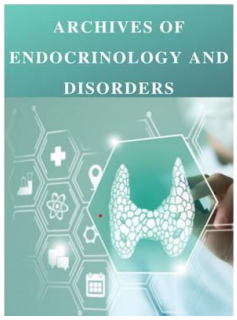

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Review Article

Graves Disease in the COVID-19 Era: Incidence Signals, Diagnostic Pitfalls and Practical Lessons for Clinicians

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Abstract

Background: Since early 2020, clinicians have reported Graves Disease (GD) diagnoses temporally linked to SARS-CoV-2 infection and vaccination, raising questions about true changes in GD incidence versus shifts in recognition, testing and referral.

Objective: To synthesize peer-reviewed evidence on GD recognition and incidence during and after the COVID-19 pandemic, disentangling infection-related signals from vaccine safety data and summarizing implications for diagnosis and management.

Methods: Narrative review of PubMed/MEDLINE and Google Scholar through September 20, 2025, including population-based studies, center-based cohorts, systematic reviews and mechanistic reports; reference lists were hand-searched. Emphasis was placed on study design, confounding and risk windows.

Results: Multiple pediatric and some adult center-based cohorts reported higher rates of new GD diagnoses during the pandemic, with more symptomatic or biochemically severe presentations at diagnosis in youth. By contrast, large population-based analyses have not detected an increased incidence of post-vaccination GD or hyperthyroidism. Case reports and small series describe GD occurring after SARS-CoV-2 infection or vaccination; these clarify clinical phenotypes but cannot estimate risk. Mechanistic studies demonstrate ACE2 expression in thyrocytes and SARS-CoV-2 material in thyroid tissue, supporting plausibility for infection-related thyroid autoimmunity.

Conclusion: Evidence supports pandemic-era increases in recognized GD in several cohorts, especially the pediatric ones susceptible to ascertainment and referral bias. Population-level data do not implicate COVID-19 vaccination in increasing incident GD. Clinicians should maintain a broad differential for post-COVID hyperthyroidism, confirm GD with TRAb when possible and continue guideline-concordant management while reassuring patients regarding vaccine safety.

Keywords: Graves Disease; SARS-CoV-2; COVID-19; Vaccination

Introduction

Graves Disease (GD) is the most common cause of hyperthyroidism and a prototypical organ-specific autoimmune disease. Pre-pandemic population-based estimates from high-income settings typically range from about 20 to 50 cases per 100,000 person-years, with marked female predominance and variation by iodine sufficiency and age [1]. The COVID-19 pandemic produced unprecedented disruptions to exposure patterns (infection, stress), care-seeking, laboratory access and referral pathways, alongside intense pharmacovigilance for vaccine adverse events. Reports of GD temporally following SARS-CoV-2 infection or vaccination have prompted clinicians to ask two practical questions: (i) did GD incidence or recognition meaningfully change during the pandemic and (ii) do COVID-19 vaccines increase GD risk?

At the same time, basic and translational observations provided plausible biological avenues for thyroid involvement in COVID-19, including Angiotensin-Converting Enzyme 2 (ACE2) transcript expression in human thyrocytes and detection of SARS-CoV-2 genetic material and antigens in thyroid tissue from autopsy series [2-4]. These insights could explain thyroiditis during or after infection and, in predisposed individuals, potential perturbations of immune tolerance at the TSH receptor. However, such mechanisms do not automatically translate to vaccine exposure, which lacks a replicating virus. This narrative review synthesizes the peer-reviewed evidence up to September 20, 2025, with attention to study design and bias, to guide practical clinical decisions.

Methodology

I searched PubMed/MEDLINE and Google Scholar for English-language articles from January 1, 2020, through September 20, 2025, using combinations of terms including "Graves disease," "hyperthyroidism," "COVID-19," "SARS-CoV-2," "vaccination," "incidence," "cohort," and "self-controlled case series." We prioritized population-based studies, multi-center cohorts and systematic reviews; center-based series, mechanistic studies and illustrative case reports were included when informative. Reference lists of relevant papers were screened for additional citations. Because this is a narrative rather than a systematic review, formal risk-of-bias scoring was not performed; instead, methodological limitations are discussed within each evidence domain.

Pre-Pandemic Epidemiology of Graves Disease

Across European registry-based analyses and other high-income health systems, GD incidence estimates often lie between ~20 and 50 per 100,000 person-years, with sex ratios favoring females and mid-adult predominance [1]. These baselines frame the interpretation of pandemic-era signals.

Pandemic-Era Clinical Recognition Patterns

Signals of increased GD diagnoses emerged primarily from center-based analyses-especially in pediatrics. A U.S. pediatric endocrine center reported a doubling of new GD diagnoses in 2020-2021 versus 2018-early 2020, with more symptomatic presentations (elevated heart rate and blood pressure) and more frequent beta-blocker initiation at diagnosis [6]. A New York pediatric cohort likewise observed a significant increase in new-onset GD during the pandemic with temporal alignment to community COVID-19 surges [7]. In adults, a Spanish tertiary-center study comparing 2017-2019 with 2020-2021 found a higher number of incident GD cases in 2021 and seasonality coinciding with pandemic dynamics [5]. These studies are susceptible to ascertainment and referral biases (e.g., threshold for testing, clinic access) but collectively suggest an uptick in recognized GD during the pandemic, particularly among youth.

Post-Infection Graves Disease and Thyroid Outcomes

Case reports and small series document new-onset or relapsed GD after SARS-CoV-2 infection, frequently with TRAb positivity when measured, clarifying the clinical phenotype but not quantifying risk [8,9]. Cohort-level data on thyroid outcomes after infection are heterogeneous, with differences in outcome definitions, risk windows and confounding control; thus, precise infection-attributable GD incidence remains uncertain. Clinicians should consider GD in the differential of post-COVID thyrotoxicosis while also evaluating for destructive thyroiditis.

COVID-19 Vaccination and Risk of Graves Disease

The most robust evidence comes from population-based designs. In Hong Kong (≈2.3 million vaccine recipients; mRNA and inactivated platforms), a self-controlled case series found no increase in incident hyperthyroidism, hypothyroidism, GD or thyroiditis within 56 days after vaccination [10]. In Israel, a population-based matched case-control study focused specifically on incident GD found no association between vaccination and GD risk [11]. A US single-center pre/post study similarly detected no increase in new GD incidence after mRNA vaccine rollout [12]. A longitudinal analysis assessing longer-term thyroid outcomes after vaccination reported mixed signals across thyroid endpoints that require replication and do not specifically implicate GD pathogenesis [13].

By contrast, systematic reviews aggregating case reports have compiled dozens of post-vaccine GD cases worldwide; these provide important clinical details (including an early-onset phenotype) but, by design, cannot estimate incidence or establish

causality [14,15]. Taken together, population-based studies outweigh case series and do not support an increased population-level risk of incident GD attributable to vaccination.

Mechanistic Plausibility: Infection Versus Vaccination

Three complementary observations support plausibility for infection-related thyroid autoimmunity: ACE2 transcript expression in human thyroid follicular cells, cytokine-mediated up-regulation of ACE2 in primary thyrocytes and detection of SARS-CoV-2 RNA/antigens in thyroid tissue from autopsy series [2-4]. These findings make infection-triggered thyroiditis and potential breaks in tolerance plausible. However, they do not imply equivalent risk from vaccination, which exposes the immune system to antigen without replicating virus.

Diagnostic Considerations and Practical Clinical Guidance

Post-COVID hyperthyroidism warrants a structured work-up to distinguish GD from subacute or painless thyroiditis. When available, TRAb testing is recommended to confirm GD; thyroid ultrasound (with Doppler) and where feasible, scintigraphy can assist differentiation of hyperfunction from destructive processes. Management should follow guideline-concordant care, including consideration of beta-blockade for symptomatic control and selection among antithyroid drugs, radioiodine or surgery based on patient factors and preferences [18]. Pediatric management should follow dedicated guidance emphasizing methimazole over propylthiouracil, longer antithyroid drug courses and specialized input for definitive therapy [17]. In counseling, clinicians can reassure patients that large studies do not indicate an increased incidence of GD after vaccination while acknowledging that rare post-vaccine GD has been described and is generally manageable (Table 1,2).

Study	Setting/Period	Population	Design	Key Findings
Donner, et al., [6]	U.S. pediatric tertiary center; 2018-2021	Youth (0-18 years)	Retrospective chart review	Increased new GD in 2020-2021 vs 2018-early 2020; more symptomatic at presentation; more beta-blocker use.
Pollack-Schreiber, et al., [7]	New York, USA; pre-pandemic vs pandemic era	Children and adolescents	Retrospective cohort	Significant increase in incident pediatric GD with temporal association to community COVID-19 surges.
Barajas-Galindo, et al., [5]	León, Spain; 2017-2019 vs 2020-2021	Adults >18 years	Cross-sectional, single center	Higher number of incident GD in 2021; seasonality aligning with pandemic dynamics; potential referral/testing effects.

Table 1: Center-based studies reporting increased recognition of Graves disease during the COVID-19 pandemic.

Study	Design/Setting	Vaccines	Outcomes	Main Result
Wong, et al., [10]	Self-controlled case series; Hong Kong (~2.3M recipients)	BNT162b2 (mRNA), CoronaVac (inactivated)	ATD/L-T4 initiation, biochemical hyper/hypothyroidism, GD, thyroiditis	No increased risk within 56 days after doses.
Gorshtein, et al., [11]	Population-based matched case-control; Israel	mRNA predominant	Incident GD	No association between vaccination and GD incidence.
Endo, et al., [12]	Single-center pre/post	mRNA rollout	New GD diagnoses	No increase in new

	comparison; USA	period		GD after vaccine rollout; described early-onset phenotype subset.
Cheng, et al., [13]	Longitudinal cohort; administrative data	Mixed	Long-term thyroid outcomes	Mixed thyroid outcome signals; findings do not specifically implicate GD pathogenesis; require replication.

Table 2: Population-based studies evaluating COVID-19 vaccination and thyroid outcomes.

Limitations of the Evidence Base

Most incidence signals arise from single-center or regional comparisons and are vulnerable to ascertainment and referral biases and to unmeasured confounding (pandemic stress, co-infections). Vaccine-safety studies rely on coding and constrained risk windows and may miss subtle phenotypes; nevertheless, they provide the best available denominator-based evidence. Future linkage studies integrating laboratory data, prescriptions, imaging and confirmed infection/vaccination timing are needed to precisely quantify infection-attributable GD risk and to characterize long-term outcomes.

Conclusion

Pandemic-era cohorts, especially pediatric ones, show increased recognition of GD, while large population-based analyses do not implicate COVID-19 vaccination in raising incident GD risk. Mechanistic data support plausibility for infection-triggered thyroid involvement. Clinicians should continue standard GD evaluation and management, remain vigilant for GD after infection and provide balanced counseling on vaccine safety.

Conflict of Interest

The authors declare that they have no conflict of interest.

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